

**FORMULATIONS AND EVALUATION OF  
ORO DISPERSIBLE TABLETS OF LAFUTIDINE  
BY DIRECT COMPRESSION METHOD**

**A DISSERTATION SUBMITTED TO  
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**MASTER OF PHARMACY  
IN  
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**Submitted By**

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**MAY-2018**

**CERTIFICATE**

## **CERTIFICATE**

This is to certify that the dissertation entitled “**FORMULATIONS AND EVALUATION OF ORAL DISPERSIBLE TABLETS OF LAFUTIDINE BY DIRECT COMPRESSION METHOD**” is a bonafide work done by **Mrs.S.SIVA PRIYA** (Reg.No261611307), Madurai Medical College in partial fulfilment of the University rules and regulations for award of Master of Pharmacy (II Year, Pharmaceutics) under my guidance and supervision during the academic year 2017-2018.

**Name & Signature of the Guide**

**Name & Signature of the Head of the Department**

**Name & Signature of the Dean / Principal**

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## ACKNOWLEDGEMENT

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**Place: Madurai**

**Date:**

**Mrs.S.SIVA PRIYA**

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# CHAPTER I

## INTRODUCTION

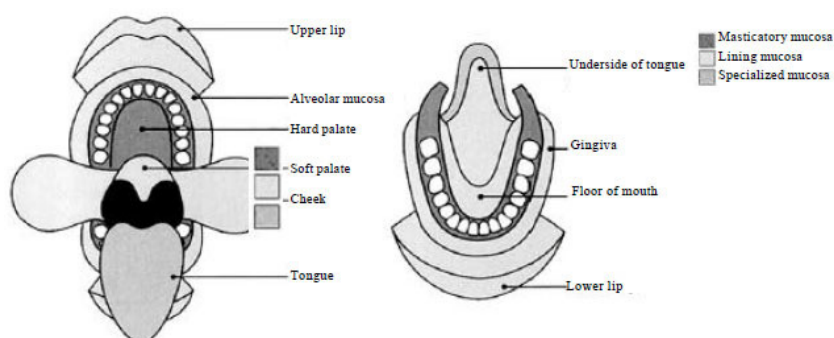
## CHAPTER I

## ORAL MUCOSA DRUG DELIVERY SYSTEM

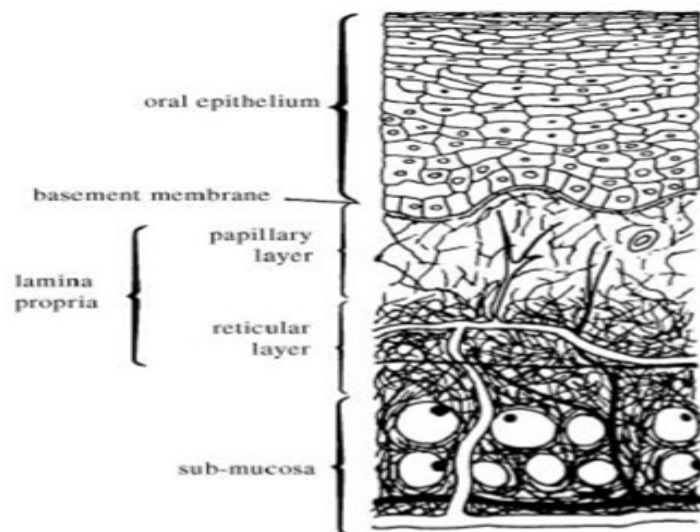
Oral routes of drug administration have wide acceptance up to 50-60 % of total dosage forms. Solid dosage forms are popular because of ease of administration, acute dosage, self-medication, pain avoidance and most importantly the patient compliance.

The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficult to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention, or dispersible tablets are not indicated for people who have swallowing difficulties, but also are ideal for active people.

Fast dissolving tablets are also called as mouth-dissolving tablets; melt in mouth tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving etc., (DebjitBhowmik, Chiranjib. Et., 2009).



The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelium cells increase in size and become flatter as they travel from the basal layers to the superficial layers (Amir. H Shajaeietal., 1998).



The turnover time for the buccal epithelium has been estimated at 5-6 days, and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 $\mu$ m, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200  $\mu$ m. The composition of the epithelium also varies depending

on the site in the oral cavity. The mucosae of areas subject to mechanical stress (The gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and only have small amounts of ceramide. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosylceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: The time of day, the type of stimulus, and the degree of stimulation. The salivary PH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the PH. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral trans mucosal drug delivery systems is this water rich environment of the oral cavity ( Amir H.shojaei et al.,1998).

**ORAL DISSOLVING TABLETS**

Oral dissolving tablets defined as a solid dosage form conflict nearly 35% of the general population. To solve the above mentioned problem, pharmaceutical technologists have put in their best efforts to develop a fast dissolving drug delivery i.e. Fast dissolving tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. A Fast dissolving tablet usually dissolves in the oral cavity within 15 seconds to 3 minutes. Most of FDTs include certain super disintegrants and taste masking agents. Fast dissolving tablets have formulated for paediatric, geriatric, and bedridden patients (Arijit Gandhi et al, and Errolla Mahesh et al.,2012).

Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. Their growing importance was underlined recently when European pharmacopoeia adopted the term “orodispersible tablet” as a tablet that to be placed in the mouth where it disperse rapidly before swallowing. The bioavailability of some drugs maybe increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach (Mohit Mangalet al., 2012).

**CRITERIA FOR ORAL DISSOLVING DRUG DELIVERY**

- Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.
- Allow high drug loading. Be compatible with taste masking and other excipients.
- Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
- Exhibit low sensitivity to environmental conditions such as humidity and temperature.
- Be adaptable and amenable to existing processing and packaging machinery.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- Leave minimal or no patients who refuse to swallow a tablet, such as paediatric and geriatric patients and psychiatric patients.
- Convenience of administration and accurate dosing as compared to liquid.
- Allow the manufacture of tablets using conventional processing and packaging equipment's at low cost (DebiitBhowmik et al., 2009 and Sharma Deepak et al ., 2012).

**ADVANTAGES:**

- Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bed ridden patients.
- Patient's compliance for disabled bed ridden patients and for travelling and busy people who do not have ready access to water.
- Good mouth feel property of Mouth dissolving drug delivery system helps to change the basic view of medication drugs.
- Convenience of administration and accurate dosing as compared to liquid formulations.
- Benefit of liquid medication in the form of solid preparation.
- More rapid drug absorption from the pregastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action.
- Pre-gastric absorption can result in improved bio-availability, reduced dose and improved clinical performance by reducing side effects.
- New business opportunity produced differentiation, line extension and lifecycle management, exclusivity of product promotion and patent-life extension.
- The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- Beneficial in cases such as motion sickness (kinetosis). sudden episodes of allergic attack or coughing, where an ultra- rapid onset of action required (Arijit Gandhi et al.,2012).

**LIMITATIONS OF MOUTH DISSOLVING TABLETS:**

- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.

**DRUG SELECTION CRITERIA:**

- The ideal characteristics of a drug for Mouth Dissolving tablet include.
- Ability to permeate the oral mucosa.
- At least partially non-ionized at the oral cavity pH.
- Have the ability to diffuse and partition into the epithelium of the upper GIT.
- Small to moderate molecular weight.
- Low dose drug preferably less than 50 mg.
- Short half life and frequent dosing drugs are unsuitable for MDT.
- Very bitter or unacceptable taste and odor drug are unsuitable for MDT.
- The role of excipients is important in the formulation of mouth dissolving tablets.
- These inactive food grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents. Binders keep the composition of these mouth dissolving tablets together during the compression stage.
- Important ingredients that are used in the formulation of MDTs should allow quick release of the drug, resulting in faster dissolution. This includes both the actives and the excipients.



- Disintegration and solubilisation of a directly compressed tablet depend on single or combined effects of disintegrants, water soluble excipients and effervescent agents (Mayuri et al., 2014, and Md. Neha Siddiqui et al., 2010).

## **TECHNOLOGIES USED FOR MANUFACTURING OF MDTs**

### **1. LYOPHILIZATION OR FREEZE DRYING.**

A process in which water is sublimated from the product after freezing. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water sublimation. Lyophilization process imparts glossy amorphous structure to the bulking agent and sometimes to drug, thereby enhancing the dissolution characteristics of the formulation (Bhasin et al., 2011, Bandari et al., 2008 and Pahwa et al., 2010).

### **2. MOLDING.**

In this method, molded tablets are prepared by using water soluble ingredients so that the tablets dissolve completely and rapidly.

The powder blend is moistened with a hydro alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air drying. Molded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution (Asish et al., 2011, Bandari et al., and Pahwa et al., 2010).

### **3. COTTON CANDY PROCESS:**

This process is named as it utilizes a unique spinning mechanism to produce floss like crystalline structure, which mimics cotton candy.

process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning.

The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to MDTs (Alok Kumar Gupta et al., 2011, and Shukla et al., 2009).

#### **4. SPRAY DRYING**

Spray drying can produce highly porous and fine powders that dissolve rapidly. The formulations are incorporated by hydrolysed gelatins as supporting agents, mannitol as bulking agents, sodium carboxymethyl cellulose or crosscarmellose sodium as disintegrating and in acidic material (e.g. citric acid) and or alkali material (e.g. Sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium (Rakesh Kumar Bhasin et al., 2011 and Siraj sheikh et al., 2010).

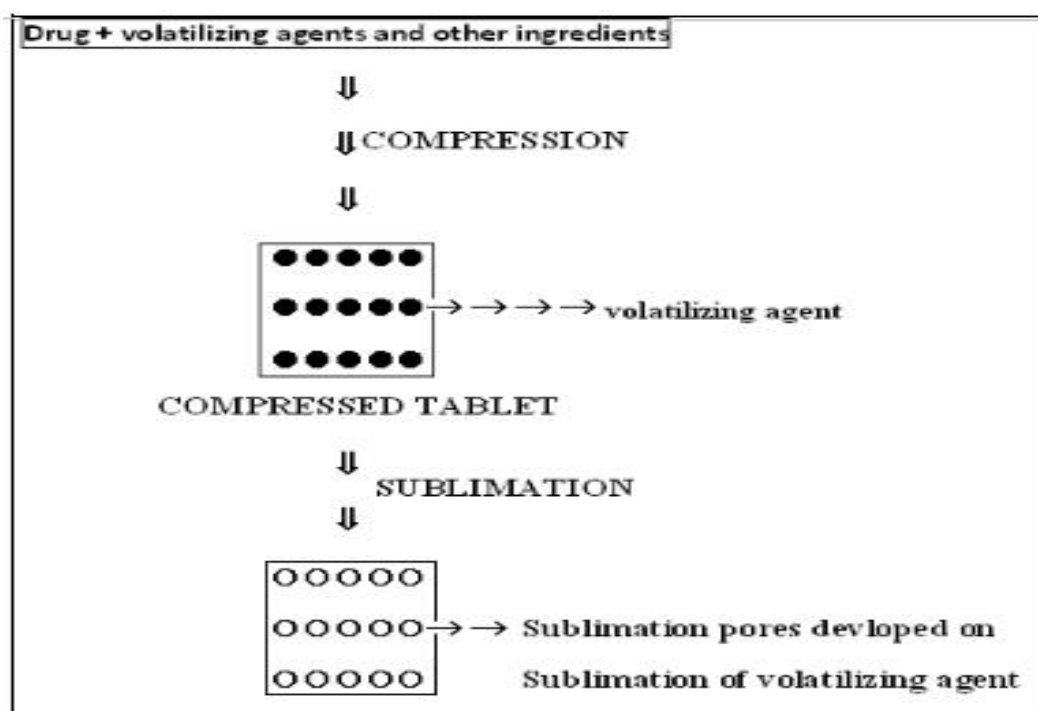
#### **5. MASS EXTRUSION**

This technology involves softening the active blend using the solvent mixture of water soluble poly ethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste (Pooja Mathur et al., 2010).

#### **6. SUBLIMATION.**

The slow dissolution of the compressed tablet containing even highly water soluble ingredients is due to the low porosity of the tablets. Inert solid

ingredients that volatilize readily (e.g. Urea, ammonium bicarbonate, hexa methylene tetramine, camphor etc ) were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structure additionally, several solvents (e.g. cyclohexane, benzene) can be also used as pore forming agents (Ashish.P et al.,2011, bandari et al., 2008 and kumar et al.,2012).



## 7. NANONIZATION

A recently developed nanomelt technology involves reduction in the particle size of drug to nanosize by wet milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilisers, which are then incorporated into MDTs. This technique is mainly advantageous for poor water soluble drugs and also for a wide range of doses (to 200mg of drug per unit) (Gupta. A et.al., 2010 and Kamal Saroha et.al.,2010).

## 8. DIRECT COMPRESSION

Direct compression method is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production method. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrates, water soluble excipients and effervescent agent (**Deepak Bhowmik et al., 2009, Kumar et al., 2012 and Bhasin et al., 2011**).

- A. Superdisintegrants: in many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.
- B. Sugar based Excipients: the use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display water soluble and pleasing mouth feel.

## PATENTED TECHNOLOGIES FOR FAST DISSOLVING TABLETS

1. Zydis Technology
2. Orasolv Technology
3. Durasolv Technology
4. Flash dose Technology
5. Shear form Technology

6. Wow tab Technology
7. Flash tab Technology
8. Dispersible tablet Technology
9. Frosta Technology
10. Pharm burst Technology
11. Oraquick Technology
12. Quick dis Technology
13. Nano crystal Technology
14. Zipllets/ Advatab Technology
15. Ceform Technology
16. Quicksolv Technology
17. Lyo Technology

### **1. Zydis technology**

Zydis is the first mouth dissolving dosage form in the market. Zydis matrix is made up of a number of ingredients in order to obtain different objectives. Polymers such as gelatin dextran or alginates are added to impart strength during handling. This form a glossy and amorphous structure. This technology involves softening the active blend using the solvent mixture of water soluble poly ethylene glycol using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste (**Tejvirkaruret.al., 2011**).

**Drawback:**

- A. Water insoluble drug can be incorporated only up to 400mg per tablet or less.
- B. Fragility and poor stability.

**2. OROSOLV TECHNOLOGY.**

Orosolv technology has been developed by “CIMA” tabs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system (Srivastava saurabh et al., 2012 and Nishtha Tiwari et al., 2012).

**3. Durssolv Technology.**

Durosolv is the patented technology of “Cima” labs. The tablets made by this technology consist of a drug, fillers and lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. Durisol is an appropriate technology for products requiring low amounts of active ingredients (Ashish. P. et al., 2011 and Rajashree Panigrahi et al., 2010).

**4. FLASHDOSE TECHNOLOGY.**

Flashdose technology has been patented by “FUIS” nurofen meltlet, a new form of ibuprofen as melt in mouth tablets, prepared using flashdose technology is the first commercial product launched by “Bisavail Corporation”. Flash dose tablets consist of self binding sheraform matrix termed as “FLOSS”.

Shear form matrices are prepared by flash heat processing (**Alokkumar Gupta et al., 2011 and PoojaMathur et al., 2010**).

#### **5. SHEARFORM TECHNOLOGY.**

It's based on preparation of floss that is known as shear form matrix, which is produced by subjecting a feedstock containing a sugar carrier by flash heat processing. In this process, sugar is simultaneous subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal, flow condition, which permits part of it to move with respect of mass. The flowing mass exists through the spinning head they flings the floss. The floss so produced is amorphous in nature so it is further chopped and recrystallised by various techniques to provide uniform flow properties and thus facilitate blending. The recrystallised matrix is than blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet. The active ingredient and other excipients can be blended with floss before carrying out recrystallization. The shearform floss when blended with the coated or uncoated microsphereres, is compressed into flashdose or EZ chew tablets (**Srivastava Saurabh et al.,2012 and Harendra et al., 2014**).

#### **6. WOWTAB TECHNOLOGY.**

Yamanouchi's WOWTABR (without water) technology employs a combination of saccharides to produce fast dissolving tablets using conventional granulation, blending drying and direct compression of tablets. Taste masking is provided by the combination of one or more sugar like excipients or microencapsulation of the active ingredients. These tablets exhibit significant hardness allowing packaging in conventional bottles or blisters (**Harendra et al., 2014**).

**7. FLASHTAB TECHNOLOGY.**

Program pharm laboratories have patented the flashtab technology, Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules maybe prepared by using the conventional techniques like coacervation, micro encapsulation and extrusion spheronisation. All the processing utilized conventional tableting technology.

**(Aloe Kumar Gupta et al., 2012).**

**8. DISPERSIBLE TABLET TECHNOLOGY**

Lek, Yugoslavia patents this technology. It offers development of MDTs with improved dissolution rate by incorporating 8-10%of organic acids and disintegrating agents. Disintegrating agent facilitates rapid swelling and good wetting capabilities to the tablets that results in quick disntergration. disintegrants include starch, modified starches, microcrystalline cellulose, alginic acid, cross linked sodium carboxy methyl Cellulose and cyclodextrins combination of disintegrants improves disintegration of tablets usually less than 1 minute **(Aloe Kumar Gupta et al., 2012).**

**9. FROSTA TECHNOLOGY.**

This technology patents by akina. It utilizes the concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. Plastic granules composed of: porous and plastic material, water penetration enhancer and binder .the process involves usually mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintrgration time ranging from 15 to 30 Sec depending on size of tablet.



**10. PHARAMABURST TECHNOLOGY.**

SPI pharma, new castle, patents this technology. It utilizes the co processed excipients to develop MDTs, which dissolves within 30-40 s. this technology involves dry blending of drug, flavor, and lubricants followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles. **(Harendra et al.,2014)**

**11. OROQUICK TECHNOLOGY.**

The oraquick ODT formulation utilizes a patented taste masking technology by KV pharmaceutical company, who claims that its taste masking technology ie. Microsphere technology (micromask) has superior mouth feel over taste masking alternatives. The taste masking process does not utilize solvents of any kind and therefore leads to faster and superior efficient production. Tablet with significant mechanical strength without disrupting taste masking are obtained after compression. Oraquick claims quick dissolution in matter of seconds with good taste masking. There are no products yet in the market using oraquick Technology, but KV pharmaceutical has products, having different classes of drugs such as analgesics, cough and cold, psychotics and anti infective, in developmental stage **(Sharma Deepak et al., 2012).**

**12. QUICK-DIS TECHNOLOGY.**

Lavipharm has invented an ideal intra-oral mouth dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intra-oral drug delivery system, trademarked quick-dis™, is Lavipharm™ Proprietary patented technology and is a thin flexible, and quick dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application

and rapidly releases the active agent for local and or systemic absorption. The typical disintegration time is only 5 to 10 seconds for the quick-Dis TM film with a thickness of 2mm. the dissolving time is around 30 seconds for quick DisTM film with a thickness of 2mm **(Deepack et al., 2012)**.

### **13. NANOCRYSTAL TECHNOLOGY.**

This is patented by Elan, king of Prussia. Nano crystal technology includes lyophilization of colloidal dispersions of drug substance and water soluble ingredients filled into blisters pockets. This method avoids manufacturing process such as granulation, blending and tableting which is more advantages for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drug **(Tejvirkaur et al., 2011)**

### **14. ZIPLETS/ADVATAB TECHNOLOGY.**

It utilizes water insoluble ingredient combined with one or more effective disintegrants to produce MDT with improved mechanical strength and optimal disintegration time at low compression force.

### **15. CEFORM TECHNOLOGY.**

This technology involves preparation of microspheres of active drugs. Drug material alone or in combination with other pharmaceutical substance and excipients is placed into a precision engineered rapid spinning machine. The centrifugal force comes into action, which throw the dry blend at high speed through small heated openings. Due to the heat provided by carefully controlled temperature, drug blend liquefies to form asphere, without affecting the drug stability. The microspheres are thus formed are compressed into tablets. As the drugs and excipients both can be processed simultaneously, it create a unique

micro environment in which the material can be incorporated into the microspheres that can alter the characteristics of the drug, such as enhancing solubility and stability (**Swami M. Velmanickam et al., 2010**).

#### **16. QUICKSOLV TECHNOLOGY.**

This technology used two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.

#### **17.LYO TECHNOLOGY**

Lyo technology is patented by pharmalyoc. Oil in water emulsion is prepared and placed directly into blister cavities followed by freeze drying. Non homogeneity during freeze drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered (**Srivastava Saurabh et al., 2012 and Deepak et al.,2012**).

#### **INGREDIENTS TO BE USED FOR ORAL DISINTERGRATING TABLET**

Important ingredients that are used in the formulation of fast disintegrating tablets should allow quick release of the drug, resulting in faster dissolution. This includes both the active and inactive ingredients excipients balance the properties of the actives in fast disintegrating tablets.

##### **Binders:**

The choice of a binder is critical in a fast dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredients. Binders keep the composition of these fast

dissolving tablets together during the compression stage. The right selection of a binder or combination of maintain the integrity and stability of the tablet. Binders can either be liquid, semisolid, solid or mixtures of varying molecular weights such as poly ethylene glycol. As binding capacity of the binder increases, disintegrating time of the tablet increases and this counter act the rapid disintegration.

**Lubricants:**

Lubrications are used for to reduce the friction during compaction and ejection of tablets in present study magnesium stearate and talc were used as lubricant e.g. stearic acid, magnesium stearate, poly ethylene glycol, liquid paraffin, magnesaiumlaulylsulfate(**Brahma Reddy D.R et al., 2011**).

**Bulking agent:**

The material contributes functions of a diluents, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentrations of the active in the composition. The recommended bulking agents for this delivery system should be more sugar based such as mannitol, poly dextrose, lactate and starchhydrolysate for higher aqueous solubility and good sensory perception.

**Flavors and Sweeteners:**

Flavors are peppermint, aromatic oil, clove oil, anise oil, eucalyptus oil, thyme oil, vanilla oil, and citrus oil. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Formulators can choose from a wide range of sweeteners including sugar,

dextrose and fructose, as well as non nutritive sweeteners such as aspartame, sugar alcohols and sucralose (**Brahma Reddy D.R et al., 2011**).

#### **Role of superdisintegrants:**

A “Superdisintegrants” is an excipient, which is added to tablet or capsule blend to aid in the breakup of the compacted mass, when put in to a fluid environment. Superdisintegrants improve disintegration dissolution of the tablets. It is essential to choose an optimum concentration of superdisintegrants so as to tablets. Superdisintegrants, provide rapid disintegration due to combined effect of swelling of superdisintegrants the wettability of the carrier increases, this promoted the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. The optimum concentration of the superdisintegrants can be selected according to the critical concentration of the disintegrants. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs (**HardikShihora et al., 2011 and Sharma Deepak et al., 2012**).

#### **FACTORS AFFECTING ACTION OF DISINTEGRANTS**

- Percentage of Disintegrate Present in The Tablets
- Type of Excipients Present In The Tablets
- Combination of disintegrants
- Presence of surfactant
- Hardness of tablet
- Nature of drug substance

- Mixing and screening

**Ideal characteristics of superdisintegrants:**

- Poor gel formation
- Good compressibility
- Inert
- Non-toxic
- Good flow Properties
- Requirement of least quantity
- Good mouth feel
- Particle size and different super disintegrants

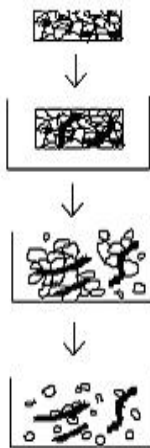
**MECHANISM OF ACTION OF SUPER DISINTEGRANTS**

The tablet breaks to primary particles by one or more of the mechanism listed below:

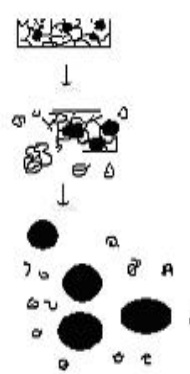
1. By swelling
2. By capillary action
3. Due to disintegrating particle /particle repulsive forces
4. Due to deformation
5. Due to release of gases

**By Swelling:**

1. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high. Fluid is unable to penetrate in the tablet and disintegration is again slows down.

**WICKING**

Disintegrant pulls water into the pores and reduces the physical bonding forces between particles

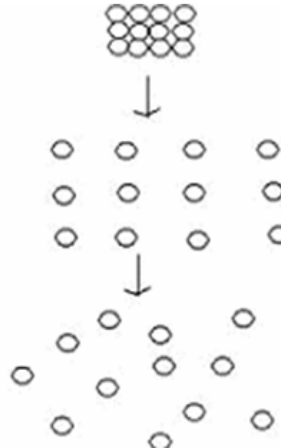
**SWELLING**

Particles swell and break up the matrix from within, swelling sets up. Localized stress spreads through out the matrix

### Mechanism of action of superdisintegrants by swelling

**DEFORMATION**

Particles swell to pre – compression size and break up matrix

**REPULSION**

Water is drawn into pores and particles repel each other due to the resulting electrical force

### Disintegration of tablet by deformation and repulsion

**2. By Capillary Action:**

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air absorbed on the particles, which weakens the intermolecular bond and breaks the tablet into particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

**3. Due to Disintegrating Particle/Particle Repulsive Forces:**

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non swelling particle also caused is integration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

**4. Due to Deformation:**

Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. Disintegration of tablet by repulsion: Another mechanism of disintegration attempts to explain the swelling of tablet made with "non swellable" disintegrants. Guyot Hermann has proposed a particle repulsion theory based on the observation that no swelling particle also causes



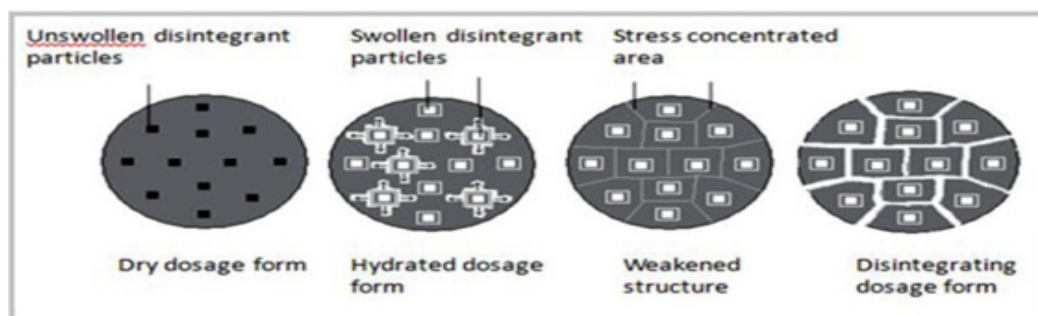
disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that the methods of incorporating disintegrants into tablets. This increase in size of the deformed particles produces a breakup of the tablet. This maybe a mechanism of starch and has only recently begun to be studied (**Tejvir Kaur et al., 2011**)

#### **5. Due to Release Of Gases:**

Carbon-dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid and tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added into two separate fraction of formulation (**NishthaTiwari et al., 2012**).

#### **6. By Enzymatic Action:**

Here, enzymes present in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.



**Figure.7. Disintegration Mechanism Of Superdisintegrant Materials**

#### **Internal Addition (Intragranular):**

In internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules. In dry granulation method, the disintegrant is added to other excipients before compressing the powder between the rollers.

#### **External Addition (Extra granular):**

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression.

#### **Partly Internal and External:**

In this method, part of disintegrant can be added internally. This results in immediate disruption of the tablet into previously compressed granules while the disintegrating agent within the granules produces additional erosion of the granules to the original powder particles. This method can be more effective. If both intragranular and extragranular methods are used, extragranular portion break the tablet into granules and the granules further disintegrate by intragranular portion to release the drug substance into solution. However, the portion of intragranular disintegrant (in wet granulation processes) which reduces the activity of the disintegrant. The intragranular disintegrant tends to

retain good disintegration activity in case of compaction process as it does not involve its exposure to wetting and drying (**MohitMangal et al., 2012**).

### **Selection Criteria for Superdisintegrant**

Although superdisintegrants primarily affect the rate of disintegration, but when used at high levels it can affect mouth feel, tablet hardness and friability. Hence, various ideal factors to be considered while selecting an appropriate superdisintegrants for a particular formulation should:

1. Proceed for rapid disintegration, when tablet comes in contract with saliva in the mouth/oral cavity.
2. Be compactable enough to produce less friable tablets.
3. Produce good mouth feel to the patients. Thus, small particle size is preferred to achieve patient compliance.
4. Have good flow, since it improves the flow characteristics of total blend (**Vimal V.V.et.al.,2013**).

# CHAPTER II

## LITERATURE REVIEW

## CHAPTER II

### LITERATURE REVIEW

**Gupta M.M. et al., 2014**, formulated and evaluated fast disintegrating combination tablet of levocetirizinedihydrochloride and mentelukast sodium by using direct compression method. The tablets were prepared using micro crystalline cellulose as diluent along with crospovidone, croscarmellose sodium and sodium starch glycolate as a super distegrants. The disintegration time and dissolution study and it was concluded that the tablet formulation prepared with 2% CCS showed better distintegration time in comparison with other formulation.

**Sateesh Kumar Vemula et cl., 2014**, formulated and evaluated oral dispersible tablets of the meclizine hydrochloride using sublimation method to enhance the dissolution rate, with the help to superdisintegrants and camphor as sublimating agent, the formulation with crospovidone used as superdisintegrants exhibited fast release profile of about 98.61% in 30 min with 47 sec when compared with other formulations and marketed tablet.

**Nagendrakumar. D et al., 2014**, formulated and evaluated oral dispersible tablets of metoclopramide hydrochloride developed by the direct compression method using different concentrations of crospovidone (1.5% - 7.5%) as synthetic superdisintegrant and isolated mucilage of hibiscus rosasinensis (1.5% - 7.5%) as natural superdisintegrant. Results revealed that the formulation containing 7.5% of crospovidone and formulation containing 7.5% of hibiscus rosasinensis was found to be promising formulation.

**Subbiah B.V. et al., 2014**, formulated and evaluated oral dispersible tablets by direct compression method using trihexyphenidyl hydrochloride as a model drug. Oral dispersible tablets of trihexyphenidyl hydrochloride formulated using different concentration of superdisintegrants like sodium starch glycolate and crospovidone. The formulation prepared with sodium starch glycolate as superdisintegrants in the concentration of 6% w/w shows rapid disintegration and 99.9% of drug released within 35 min when compared with other disintegrants used in.

**SaiPadmininBolla et al., 2014**, the development of oro-dispersible tablets of clonazepam using natural superdisintegrants like Mucilage of hibiscus rosasinensis leaf and seeds of ocimumbasilicum were extracted, evaluated for the organoleptic, physicochemical parameters. The dried mucilage was used as superdisintegrant for the preparation of orodispersible tablets by direct compression method. The optimized formulation was subjected to wet granulation using PVP in IPA as the dry binder. The tablets containing 5% w/w dried mucilage of ocimumbasilicum was found to be the best formulation which disintegrated in 22 sec with 99.8% drug release.

**Ameer S.Sahib et al., 2013**, formulated and evaluated oral dispersible tablets of phenobarbital is an antiepileptic drug used in the treatment of epilepsy. Oral dispersiblephenobarbitone tablets were prepared using direct compression method technique depends on using three different superdisintegrants with different concentrations (5-15% w/w) i.e., sodium starch glycolate, croscarmellose, crospovidone. Cropovidone 10% with microcrystalline

cellulose (25%) gave the good acceptable friability ( $0.53 \pm 0.25\%$ ) with least disintegration time ( $12.07 \pm 0.23$  sec) and best flow property.

**Venkatesh K. et al., 2013**, baclofen is a muscle relaxant and describe as (3RS)-4amino-3-(4-clorophemyl) butanoic acid. Oral bioavailability of baclofen is around 80% and having half-life 4 hrs design of oral dispersible tablets of baclofen were prepared by direct compression and solid dispersion method. The results concluded that oral dispersible tablets of baclofen showing enhanced dissolution will lead to improved bioavailability and effective therapy using solid dispersion method.

**Tansande J.B. et al., 2013**, formulated and evaluated oral dispersible tablets of tomoxicam were prepared with natural and synthetic superdisintegrant by direct compression method. The natural superdisintegrant used were banana powder, soy polysaccharide 8% crospovidone showed disintegration time 10 seconds to 12 seconds respectively. The formulation with soy polysaccharide showed more than 90% drug release respectively. It was concluded that natural superdisintegrant has better disintegration time, more water absorption and faster drug release.

**Mahesh Gattani et al., 2013**, formulated and evaluated oral dispersible tablets of zolmitriptan. It is to co process tablet excipients by rotary evaporation method to create mixtures that can help in achieving direct compression optimum disintegration time along with required hardness & friability of orally disintegrating tablets. Co procession using of lactose with other excipients was done by rotary evaporation method using water as solvent. The co-processed

excipients were evaluated for pre compression and post compression properties.

**Mangesh M.Kumar et al., 2013**, formulated and evaluated oral dispersible tablets of atenolol were prepared by direct compression technique using two different superdisintegrants in combination by co-process mixing and physical mixing. Croscarmellose sodium and crospovidone were used as super disintegrants in combinations in the different ratio (1:1, 1:2, 1:3). Oral dispersible tablets of atenolol were prepared using the co-processed super disintegrants and evaluated for pre-compression and post compression parameters. Among the designed formulations, the formulation (CP) containing 4% w/w of co-processed super disintegrants (1:1) mixture of crospovidone and croscarmellose sodium emerged as the overall best formulation based on drug release characteristics in pH 6.8 phosphate buffer crystalline cellulose.

**Ramu. A et al., 2013**, formulated and evaluated rosuvastatin calcium is a selective and competitive inhibitor of HMG-CoA reductase, mainly used in the treatment of hypercholesterolemia, hypertriglyceridemia and atherosclerosis. Rosuvastatin poorly soluble in water was made to enhance solubility, dissolution rate and oral bio availability by formulating it as solid dispersions using various techniques with polyethylene glycol (PEG) 6000 as a carrier. Oral dispersible tablets of rosuvastatin were prepared with super disintegrants like sodium starch glycolate, croscarmellose sodium, pre gelatinized starch and mannitol from the optimized solid dispersions.

**Lavande J.P. et al., 2013**, formulated and evaluated fast/mouth dissolving tablet of olmesartanmedoxomil by direct compression method.



Olmesartanmedoxomil 20 mg using synthetic and natural superdisintegrants like, sodium starchglycolate, croscarmellose, crospovidone and plantagoovata mucilage in different concentrations (5, 7.5 and 10mg). The prepared formulations were evaluated and compared to synthetic superdisintegrant with plantagoovata showed faster release of the drug.

**VenkatchalanRajuPeetha et al., 2013**, formulated and evaluated mouth dissolving tablets of nimodipine drug prepared by using three different superdisintegrants croscarmellose sodium, sodium starch glycolate, crospovidone. Each superdisintegrant was used in different concentration like 2.5% 5% w/w, 7.5% w/w. The result concluded 7.5% w/w showed better optimum results.

**Venkateswarlu. B et al., 2013**, formulated and evaluated oral dispersible tablets of amotidine using combined approach of complexing agent and superdisintegrant by direct compression method. The super disintegrant was used in different concentration like 2.5w/w, 5% w/w, 7.5% w/w. The prepared tablets were dried under oven to evaporate the complexing agent and drug release. All the formulations disintegrated within 10-60 seconds with 99.3% drug release finding the result was concluded three formulations containing complexing agent and superdisintegrants showed better performance in disintegration and drug release profile.

**Kamal Saroha et al., 2013**, the oral dispersible tablets of amoxicillin trihydrate were prepared by direct compression technique using microcrystalline cellulose sodium starch glycolate and croscarmillose sodium used as synthetic superdisintegrants. Eight formulations were prepared using different

concentrations of superdisintegrants and were investigated for their effect on the disintegration time and dissolution rate of the tablets. It was found that tablets of batch (blend containing CCS 60mg) showed better disintegrating property as well as % drug release (99.78% within 25 min) than the most widely used.

**Abdul Hassan Sathali A. et al., 2012**, formulated and evaluated Fast dissolving tablets of lamivudine to prevent mother to child transmission (MTCT) of HIV virus in perinatal infants. The tablets were prepared by direct compression method, using various superdisintegrants like sodium starch glycolate, croscarmallose sodium, and crospovidone at various concentrations (2%-10%). From the results of post compression studies for tablets for tablets of all formulations, it was concluded that the formulation containing 10% crospovidone as superdisintegrants emerged as overall best formulation with lowest disintegration time and highest drug release rate.

**Venkata Naveen Kasagana et al., 2012**, formulated and evaluated in oral dispersible tablets of piroxicam by using three different superdisintegrants namely crospovidone, sodium starch glycolate and pre gelatinized starch with three different concentrations (3%, 4% and 5%) and (without super disintegrant) were analysed. The results revealed that the formulation containing crospovidone (5%) as super disintegrant was better one which satisfied all the requirements necessary for oral dispersible tablets.

**Mali P.A. et al., 2012**, formulated evaluated oral dispersible tablets of carbamazepine is very low solubility in biological fluid & poor bioavailability after oral administration. The tablets were prepared with the hep of super

disintegrants such as crospovidone, sodium starch glycolate & pre gelatinized starch. With effect of superdisintegrants among all formulation was considered best. The result concluded that FDT of poorly soluble drug carbamazepine, showed enhanced dissolution lead will lead to improved bioavailability, effectiveness & hence better patient compliance.

**Rajeshree Panigrahi et al., 2012**, oral dispersible tablets of lisinopril were designed using combination of synthetic superdisintegrants like croscarmellose sodium, crospovidone and sodium starch glycolate in a ratio of 5:10 and 10:5 respectively by direct compression method. The formulation of lisinopril containing 10% crospovidone and 5% croscarmellose showed disintegration time of 50 sec respectively with 99% drug release within 30 min. The results showed that superdisintegrants used in combinations exhibited better disintegrating property.

**Cinmay Anand. L et al., 2012**, formulated and evaluated oral dispersible tablet of tolfenamic acid. The solubility of tolfenamic acid was improved by co-micronized with microcrystalline cellulose and surfactants as sodium lauryl sulfate. One reference formulation was also manufactured with conventional method using non-micronized tolfenamic acid with surfactants. The formulation was then evaluated for various physical and analytical properties of rapid dispersible tablets. Results obtained showed that there was significant increase in dissolution rate of drug in first 5 minutes of time interval as compared to reference formulation. The wetting and dispersion properties of formulations also found superior as compared to reference formulation.

**AnieVijetha K. et al., 2012**, formulated and evaluated oral dispersible tablets (FDT) of isradipine by employing different technologies like liquid solid by improving wetting, sublimation by creating porous environment, effervescent and super disintegrant by breaking the tablet fast. The FDT of isradipine were also prepared by adopting direct compression method. The isradipine FDT of isradipine were also prepared by adopting direct compression method. The isradipine FDTs of effervescent technology was showing immediate release with T90% within 4 min and hence the effervescent technology was proved to be the promising in comparison with other technology types.

**SudheshnaBabuSukhavasi et al., 2012**, formulated and evaluated the oral dispersible tablets of amlodipine besylate tablets using Fenugreek seed mucilage and ocimumbasilicum gum as a natural superdisintegrating agents to achieve quick onset of action, is to increase the water uptake with in shortest wetting time and there by decrease the disintegration time of the tablets by simple and cost effective direct compression technique. The best formulations FFGK5 & FOB5 have shown good disintegration time, hardness and friability. The best formulations were also found to stable.

**DevendraRevanandRaneet et al., 2012**, formulated and evaluated oral dispersible tablets of albendazole is broad spectrum anthelmintic use against many helminths. Oral dispersible tablets prepared by direct compression method. The prepared tablets were subjected for post compressional evaluation. Among all, the formulation containing 5% w/w super disintegrantcros povidone and 20% w/w microcrystalline cellulose was considered to be best formulation, which release up to 99.097%in 40 min.

**Nilesh Jain et al., 2012**, formulated and evaluated oral dispersible tablets of ciprofloxacin using superdisintegrants like crospovidone and sodium starch glycolate. The in vitro disintegration time of the best fast disintegration tablets was found to be within 36 seconds. Tablets containing crospovidone (40%) exhibits quick disintegration time than tablets containing sodium starch glycolate. The fast disintegrating tablets of ciprofloxacin with shorter disintegration time, acceptable taste and sufficient hardness could be prepared using crospovidone and other excipients at optimum concentration.

**Swati Changdeo Jagdale et al., 2012**, The main objective of the study was to enhance the dissolution of nifedipine, a poorly water soluble drug by  $\beta$ -cyclodextrin inclusion complexation of nifedipine with  $\beta$ -cyclodextrine was 1:1. Binary complex was prepared by different methods and was further characterized using XRD, DSC and FT-IR. A saturation solubility study was carried out to evaluate the increase in solubility of nifedipine. The optimized complex was formulated into fast-dissolving tablets by using the superdisintegrants Doshion P544, pregelatinized starch, crospovidone, sodium starch glycolate and croscarmellose sodium by direct compression. The result revealed that completed the tablets showed an enhanced dissolution rate compared to pure nifedipine.

**Amit Modi et al., 2012**, formulate for FDT of diclofenac sodium by using various superdisintegrant like sodium starch glycolate, croscarmellose sodium and crospovidone (polyplasdone XL) followed by direct compression technique. It was concluded that the batch which was prepared by using combination of crospovidone and sodium starch glycolate as a superdisintegrant showed

excellent disintegration time, enhance dissolution rate better taste masking and hence lead to improved efficacy and bio availability of drug.

**Saima Erumet et al., 2011**, formulated and evaluated oral dispersible tablets of aspirin prepared by direct compression method, contained excipients that comprises of lactose, cornstarch, aerosol. The results were compared with other brands. The formulate aspirin tablets by direct compression method using fewer excipients and compared that formulation with the other brands. The studied formulation showed close resemblance with the available marketed brands.

**Chowdary K.P.R. et al., 2011**, formulated and evaluated oral dispersible tablets of nimulslide by wet granulation and direct compression method, poor solubility and dissolution rate. The developed nimulslide rapidly dissolving tablet formulated with starch phosphate by direct compression method, Tablets formulated employing starch phosphate as directly compressible vehicle. Nimulide-starchphosphate (1:2) solid dispersion is gave much hogher dissolution rates and disintegrating values when compared to others.

**Basawaraj S. et al., 2011**, formulated and evaluated of oral dispersible tablets of granisetronhydrochloride is a selective 5H<sub>4</sub> receptor antagonist, treatment of vomiting in cancer therapy. Granisetron prepared by direct compression method. The prepared tablets were evaluated for pre compressional parameter such as hardness, friability, thickness, invitro dispersion time, wetting time, water absorption ratio and it was the prepared tablets were characterised by FTIR studies.

**Chandrasekhar Patro et al., 2011**, formulated and evaluated cetirizine hydrochloride mouth oral dispersible tablets using different concentrations of super disintegrants like crospovidone, croscarmellose sodium, sodium starch glycolate by direct compression method and evaluated. The results indicated that tablets with 5% croscarmellose sodium was found to be optimized which provides maximum drug release (99%) and minimum disintegration time (less than 20 sec). Stability studies of optimized formulation revealed that formulation is stable.

**Himmat Singh et al., 2011**, formulated and evaluated mouth dissolving tablets of carvedilol. The solubility of carvedilol was enhanced with different ratios of PVP by the solvent evaporation method. Invitro release profile of solid dispersion obtained in SGF without enzymes and pH6.8 phosphate buffer indicate that 100% drug release found within 20 minutes. This solid dispersion was directly compressed into tablets using crospovidone, sodium starch glycolate, and croscarmellose sodium and potacrilin potassium in different concentration as a super disintegrant. The prepared tablets containing the solid dispersion of carvedilol were found to have sufficient strength of 2.5-4 Kg/cm<sup>2</sup> which disintegrated in the oral cavity within 21 seconds contain crospovidone (5%) as super disintegrant.

**Govind K. Chandile et al., 2011**, formulated and evaluated oral dispersible tablets of haloperidol were prepared using novel co-processed super disintegrants consisting of crospovidone and primogel in the different ratio (1:1, 1:2 & 1:3) but direct compression technique. Among all, the formulation crospovidone containing 4% w/w super disintegrant (1:1 mixture of crospovidone and primogel) was considered to be best formulation, which

release up to 99.21% in 12 min. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

**Indhumathi, D. et al., 2011**, formulated and evaluated oral dispersible tablets of fluoxetine using different super disintegrants (Sodium starch glycolate, croscarmellose, crospovidonepregelatinized starch) by wet granulation method. In vitro dissolution studies shows the release is in the following order of super disintegrantscrospovidone>pregelatinized starch >croscarmellose>sodium starch glycolate. From the study it has been found and concluded, crospovidone at a concentration of 5% w/w shows maximum in-vitro dissolution profile, this is also confirmed by in vivo pharmacokinetic studies, and hence it emerged as the overall best formulation hence suitable for preparing oral dispersible tablet of fluoxetine.

**ShireeshKiran 1, R. et al., 2010**, formulated and evaluated mouth dissolving tablets of glipizide with sodium glycolate, crospovidone and pregelatinized starch. Oral dispersible tablets of the sodium starch glycolate, crospovidone and pregelatinized starch were prepared by direct-compression method in different concentrations. Dissolution profile indicated that the complete drug release in 20 min from all the formulation tested. The oral dispersible tablet of glipizide by using the pregelatinized starch showed with excellent in vitro and in vivo dispersion time and drug and release, as compared to other formulations.

**Prameela Rani A. et al., 2010**, formulated and evaluated oral dispersible tablets metformin hydrochloride with help of isphagula husk, natural



superdisintegrants and crospovidone, synthetic superdisintegrant. The disintegration time in the oral cavity was also tested and was found to be around 10 sec. based dissolution rate, it can be rated as isphagula husk >crospovidone. Hence isphagula husk was recommended as suitable disintegrant for the preparation of direct compression melt-in-mouth tablets of metformin hydrochloride. All the dissolution parameters were calculated and compared (Glycophage). It was concluded that the tablets have a acceptable hardness, rapid disintegration in the oral cavity with enhanced dissolution rate and better patient compliance.

**Raghavendra Rao, N.G. et al., 2010**, formulated and evaluated oral dispersible of felodipine. Felodipine is practically insoluble in water prepared by direct compression method. Effect of superdisintegrants (such as croscarmellose sodium, and crospovidone) on wetting time, disintegrating time, drug content, in vitro release, and stability parameters have been studied. Tablets prepared by solid dispersion with mannitol showed higher hardness than other tablets prepared by solid dispersion with PVP and PEG. Disintegration time of tablets prepared by solid dispersion using mannitol, increased significantly ( $p < 0.05$ ). From this study, it can be concluded that dissolution rate of felodipine could be enhanced by tablets containing solid dispersion by direct compression technique. Tablets containing solid dispersion with PVP of ratio 1:4 (p3), with PEG of ratio 1:4 (E3) and with mannitol of ratio 1:9 (M4) yielded best results in terms of dissolution rate.

**Shailsh Sharma et al., 2010**, formulated and evaluated oral dispersible tablets of promethazine theoclate. The solubility of promethazine theoclate was

increased by using  $\beta$ -cyclodextrin, crospovidone, camphor for using direct compression method. The optimized tablet should be prepared with an optimum amount of  $\beta$ -cyclodextrin (3.0 mg), camphor (3.29 mg) and crospovidone (2.61 mg) which disintegrated in 30s, with a friability of 0.60% and drug release of 89% in 5 min. The optimized approach aided both the formulation of oral dispersible theoclate tablets and the understanding of the effect of formulation processing variables on the development of the formulation.

**Suhas M.K. Kode et al., 2010**, mouth dissolving tablets of losartan potassium to achieve a better dissolution rate and further improving the bioavailability of the drug. Mouth dissolving tablets prepared by direct compression and using super disintegrants like Polyplasdone XL 10, Croscarmellose sodium and Explotab in different concentration and evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content, disintegration time and in-vitro dissolution profile and found satisfactory. Among all, the formulation F3 containing 5% w/w superdisintegrant Polyplasdone XL 10 was considered to be best formulation, which release up to 99.26% in 12 min.

**Keny. R.V. et al., 2010**, mouth disintegrating tablets rizatriptan benzoate were prepared by direct compression method employing crospovidone, carboxymethylcellulose calcium, Indion 414 and Indion 234 as superdisintegrants in different ratios, either alone or in combination. The formulations used, Indion 234 > Crospovidone > carboxymethylcellulose calcium > Indion 414. The tablets containing crospovidone and calcium CMC in

combination, showed faster disintegration than tablets containing crospovidone alone, calcium CMC alone and their combinations with other superdisintegrants. Indion 414 showed comparable disintegration when used alone and in combination with Crospovidone, but fastest comparable disintegration when used alone and in combination with Crospovidone, but faster disintegration was seen in its combination with calcium CMC than with others. Indion 234 also showed satisfactory disintegration time when used alone (18-19) and in combination with Crospovidone (15-16s), compared to its combination with other superdisintegrants. Rizatriptan Benzoate release was significantly faster from all the prepared formulations as compared to marketed conventional tablet formulation. In conclusion, a taste, effective and pleasant tasting mouth disintegrating tablet, exhibiting an excellent disintegration time and dissolution profile, was formulated using a combination of crospovidone (4%) and Indion 234 (2%) as superdisintegrants. Even though the excipients employed are well known and established, they have not been used with rizatriptan benzoate for formulating mouth disintegrating tablets.

**Patel, B.P. et al., 2010**, the mouth dissolving tablets of cinnarizine were prepared by superdisintegrants addition using crospovidone, croscarmellose sodium and L-HPC in different concentration like 5%, 7.5% and 10%. There are total nine formulations were prepared and evaluated for various parameters. Formulation B9 containing L-HPC in concentration of 10% showed minimum disintegration time, wetting time as compared to other formulations. Results of dissolution studies showed that total drug was released in 6 min. The results shown that disintegration time was increased in the order of L-HPC < crospovidone < croscarmellose sodium.

**Jain C.P. et al., 2009**, formulated and evaluated oral dispersible tablets of valsartan were prepared using different superdisintegrants by direct compression method. FDT disintegrant on disintegration behaviour of tablet in artificial saliva, pH 5.8 was evaluated. Wetting time of formulations containing crospovidone was least and tablets showed fastest disintegration. The drug release from FDTs increased with increasing concentration of super disintegrants and was found to be highest with formulations containing crospovidone. The release of valsartan from FDTs was found to follow non-Fickian diffusion kinetics.

**Shailendra Kumar Singh et al., 2009**, formulated and evaluated oral dispersible tablets of omeprazole and domperidone with using pertinent disintegrants by direct compression method. The tablets were prepared using mannitol as diluent and sodium saccharin as sweetening agent along with three different levels of superdisintegrant used in kollidon CL, Ac-Di-Sol, drug and SSG. Omeprazole and domperidone were well resolved and the retention times were around 9.01 and 6.2 respectively. From the results obtained, it can be concluded that the tablet formulation prepared with 4.76% Ac-Di-Sol (internally cross linked form of sodium carboxymethylcellulose) i.e., 10 mg showed disintegration time of 15 seconds in vitro. Also the hardness, friability, dissolution rate and assay of prepared tablets (batch F7) were found to be acceptable according to standard limits.

**Kawtikar P.S. et al., 2009**, formulated and evaluated oral dispersible tablets of tizanidine hydrochloride by using eudragit E100 as a taste making agent using mass extrusion technique for preparing taste masked granules. The tablet was

prepared with three super disintegrants such as sodium starch glycolate, croscarmellose sodium and crospovidone. Disintegration in oral cavity tested was found to be 22 seconds. Other tablets were prepared by using camphor as sublimating agent. It was concluded that tablets prepared by addition of superdisintegrants has less disintegration time than those prepared by sublimation method.

**Kevin C. et al., 2008**, formulated and evaluated of oral dispersible tablets of aceclofenac poor aqueous solubility and hence poor bioavailability. The effect of various super disintegrantssuch as sodium starch glucolate, cross carmellose sodium and pregelatinished starch (Starch 1500) prepared by wet granulation method. The disintegration time of all formulation showed less than 89 seconds. Formulation containing equal amount of cross carmellose sodium and pregelatinized starch showed fastest disintegration than other formulations containing starch 1500, cross carmellose sodium and sodium starch glycolate in various proportions and the percentage drug release was 99.5 within 10 minutes.

**Udya S. Rangole et al., 2008**, formulated and evaluated rapidly disintegrating tablets of hydrochlorthiazide using different concentration (2%, 3%, 4%, and 5%) of superdisintegrants like croscarmellose sodium and crospovidone by direct compression method. Disintegration time and drug release were taken as the basis to optimize the rapidly disintegrating tablet. Crospovidone in the concentration of 4% gave fastest disintegration in 16 seconds and showed 100% drug release within 14 minutes were selected as the optimized formulation.

**SheetalMalke et al., 2007**, oxycarbazepine a new anticonvulsant drug. Oral dispersible tablets of oxcarbapazine were prepared containing Avicel pH 102 as a diluent and Ac-Di-Sol as a superdisintegrant by wet granulation process. Since the drug is poorly water soluble, drug release was tested in various media and the effect of surfactant on drug release was studied. An effective, pleasant tasting and stable formulation containing 12% Ac-Di-Sol, 25% Avicel pH 10.2 and 8.5 starch as a binder was found to have a good hardness of 4-4.5 kg/cm<sup>2</sup>, disintegration time of 28±5s and drug release of not less than 90% within 30 min. The drug release was found to be comparable to the marketed dispersible tablet.

**Shagufta Khan et al., 2007**, ondansetronhydrochloride to a rapid disintegrating tablet of the taste-masked drug. Taste masking was done by complexingondansetrone hydrochloride with aminoalkyl methacrylate copolymer (Eudragit EPO) in different ratios by the precipitation method. Drug-polymer complexes were tested for drug content, in vitro taste in simulated salivary fluid of pH 6.2, and molecular property. Complex that did not release drug in SSF was considered taste-masked and selected for formulation RDTs. The complex with drug-polymer ratio of 8:2 did not show drug release in SSF; therefore, it was selected. The polyplasdone XL-10 7% wt/wt gave the minimum disintegration time. The formulation containing spray-dried mannitol and microcrystalline cellulose in the ratio 1:1 and 7% wt/wtpolyplasdone XL-10 showed faster disintegration, within 12.5 seconds, than the marketed tablet (112 seconds). Tablets of batch F4 also revealed rapid drug release (90,60 seconds) in SGF compared with marketed formulation (90,240 seconds; P G

.01). Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity.

**Mahaja. H.S. et al., 2000**, mouth dissolve tablets of sumatriptan succinate were prepared using disintegrants, sodium starch glycolate, carboxy methylcellulose sodium and treated agar by direct compression method. The prepared tablets were evaluated for thickness, uniformity of weight, content uniformity, hardness, tensile strength, porosity, friability, wetting time, water absorption ratio, in vitro and in vivo disintegration time and in vitro drug release. The tablets disintegrate in vitro and in vivo within 10 to 16s and 12 to 18s, respectively. Almost 90% of drug were released from all formulations within 10 min. The formulations containing combination of sodium starch glycolate and carboxy methyl cellulose was found to give the best results.

**Hector Fausett et al., 2000**, formulated and evaluated develop a rapidly disintegrating calcium carbonate tablet by direct compression method. Calcium carbonate tablets were formulated on a carver press using 3 different forms of (Cal-Carb 4450 ®, Cal-Carb 4457®, and Cal-Carb 4462®). The calcium concentration was determined by an atomic absorption spectrophotometer. Scanning electron microscopy was used to evaluate the surface topography of the granules and tablets. Breakig strength of Cal-Carb4450®, Cal-Carb 4457®, and Cal-Carb 4462® tablets was in the range of 7.2 to 7.7 kg, as compared with a hardness of 6.2 kg and 10 kg for the commercially available calcium tablets citracal ® and Tums®, respectively. The disintegration time for the tablets presented in the order earlier was 4.1, 2.1, 1.9, 2.9 and 9.7 minutes, respectively. The dissolution studies showed that all formulations released 100% of the elemental calcium in simulated gastric fluid in less.

## CHAPTER III

**AIM OF WORK**



## CHAPTER III

### AIM OF THE WORK

Oral drug delivery system is most preferred administration route due to its ease of administration and better patient compliance. Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing. One important drawback of such dosage forms is dysphagia, at difficulty in swallowing is common among all age groups and more specific with pediatric and geriatric population.

To overcome this weakness, developed a novel oral dosage of oraldispersible tablets are an innovative technology, which disperse rapidly in saliva, usually in a matter of seconds, without the need of water, providing optimal convenience to the patient as compared with conventional dosage forms.

Lafutidine is a namely developed second generation of histamine H<sub>2</sub> receptor antagonist. It is used in the treatment of gastric ulcers, duodenal ulcers and gastric mucosal lesions associated with acute gastritis and acute exacerbation of chronic gastritis. Lafutidine has a receptors binding affinity which is 20 – 80 times higher than famotidine, ranitidine and cimetidine.

Lafutidine is absorbed in the upper part of small intestine, reaches gastric cells via the systemic circulation and rapidly binds to gastric cells H<sub>2</sub> – receptors, resulting in immediate inhibition of gastric acid secretion.

The objective of this present study was to develop orodispersible tablets of lafutidine using superdisintegrants by simple cost effective direct compression technique which increased rate of dissolution may leads to increase in oral bio availability.

# CHAPTER IV

## PLAN OF WORK

## CHAPTER IV

### PLAN OF WORK

**1. Preparation of Standard calibration curve**

- a. Determination of  $\lambda$  max
- b. Preparation calibration curve

**2. Pre-formulation (compatibility Studies)**

- a. Infrared spectroscopic Studies
- b. Differential scanning calorimetric studies (DSC)

**3. Pre Compressional Evaluation of Powder Blend**

- a. Angle of repose
- b. Bulk density
- c. Tapped density
- d. Carr's index
- e. Hausner's ratio

**4. Preparation of oral dispersible tablets**

Direct compression method

**5. Post compressional evaluation of oral dispersible tablets**

- a. General appearance
- b. Thickness and diameter
- c. Hardness
- d. Weight variation
- e. Friability test
- f. Drug content

- g. Wetting time
- h. Water absorption ratio
- i. In vitro disintegration test
- j. In vitro dissolution test

#### **6. Selection and evaluation of best formulation**

- a. Infra red spectroscopic studies of drug, physical mixture
- b. Differential scanning calorimetric (DSC) studies of drug and physical mixture

# **CHAPER V**

## **MATERIALS AND EQUIPMENTS**

## CHAPTER V

### MATERIALS AND EQUIPMENTS

NO	MATERIALS	DISTRIBUTORS
1	Lafutidine	Niksan pharmaceutical,Gujarat,
2	Sodium Carboxy Methyl Cellulose	Central Drug House Pvt.,Ltd.,Delhi
3	Cross Povidone	Madras Pharmaceuticals - Chennai
4	Scmc+Crosspovidone +Pregeatinized Starch	Madras Pharmaceuticals - Chennai
5	Pre gelatinised starch	Apex laboratories pvt. Ltd., Chennai
6	Microcrytline Cellulose	Central drug pvt.ltd., delhi
7	Mannitol	Nice Chemicals Pvt. Ltd., Kerala
8	Lactose	Central drug house pvt. Ltd., delhi
9	Magnesium strearate	Central drug house pvt. Ltd., delhi
10	Aspartame	Central drug house pvt. Ltd., delhi
11	Lactose	Central drug house pvt. Ltd., delhi

# **CHAPTER IV**

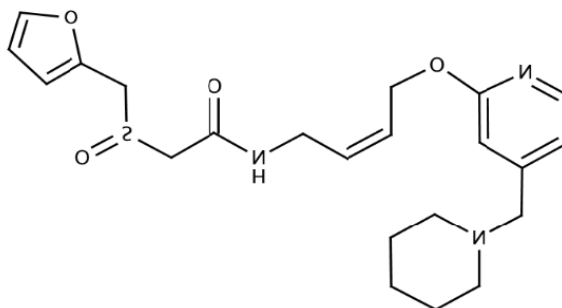
## **DRUG PROFILE**

## CHAPTER VI

### DRUG PROFILE

**Drug Name** : LAFUTIDINE

**STRUCTURE** :



<b>SOURCE</b>	:	Synthetic
<b>DESCRIPTION</b>	:	White to off-white colour powder
<b>CHEMICAL NAME</b>	:	2-(Furan-2-ylmethylsulfinyl)-N-[(Z)-4-[4-(piperidin-1-ylmethyl) pyridin-2-yl]oxybut-2-enyl]acetamide
<b>MOLECULAR WEIGHT</b>	:	431.55 g/mole
<b>MOLECULAR FORMULA</b>	:	C <sub>22</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub> S
<b>MELTING POINT</b>	:	96-104 °C
<b>SOLUBILITY</b>	:	Freely soluble in glacial acetic acid



**BIOLOGICAL DISCRIPTION:**

Histamine H<sub>2</sub> receptor antagonist. Inhibits distention-induced gastric acid secretion through an H<sub>2</sub> receptor-independent mechanism. Shows antiulcer effects in vivo. Orally active.

**PURITY** : > 99%

**STORAGE** : Stored at room temperature

**HANDLING**

Wherever possible, you should prepare and use solutions on the same day. However, if you need to make up stock solutions in advance, we recommend that you store the solution as Aliquots in tightly sealed vials at -20°C. Generally, these will be useable for up to one month. Before use, and prior to opening the vial we recommend that you allow your product to equilibrate to room temperature for at least 1 hour.

**PHARMACOKINETIC DATA**

**Protein binding** : 88%

**Half-life** : 1.92 ± 0.94 hour

**pH range** : 1- 4

**pka Value** : 3.9

**Oral bio availability** : 22-35%

**Nature** : Hydrophobic.

**Identification** : 283 nm in UV spectrophotometer

**Route of administration** : oral

**Dose** : 5mg, 10mg

**Dosage form** : tablets

**Therapeutic categories** : Second generation H<sub>2</sub> – receptor  
Antagonist

**Use** : gastric ulcers, duodenal ulcers, stomach ulcers as well as wounds in the lining of the stomach associated with acute gastritis and acute exacerbation of chronic gastritis.

### **PHARMACOKINETICS:**

#### **Blood Concentration**

When 10mg of lafutidine is orally administered to normal adult males, fasting plasma concentration of unchanged drug changed.

#### **Metabolism and Excretion:**

Within 24 hours after perioral administration of lafutidine 10mg in 6 normal adult males, the excretion rates of unchanged drug, metabolite M-4 (oxidative elimination of piperidine ring), M-7 (oxidation of piperidine ring), and M-9 (sulfonylation) in the urine are  $10.9 \pm 1.5\%$ ,  $1.7 \pm 0.2\%$ ,  $7.5 \pm 0.8\%$  and  $0.3 \pm 0.1\%$  respectively. Total excretion rate in the urine is approximately 20% of the given dosage. It has been reported that CYP3A4 is mainly (CYP 2D6 is partially) associated with the metabolism of lafutidine (in vitro). Unless reaching 3 mg/ml, no saturation of binding to protein is observed (Binding rate to human serum protein  $88.0 \pm 1.2\%$ ) (in vitro).

#### **Mechanism of Action:**

Like other H<sub>2</sub> receptor antagonists it prevents the secretion of gastric acid. It also activates calcitonin gene-related peptide, resulting in the stimulation of nitric oxide(NO) and regulation of gastric mucosal blood flow, increases somatisation levels also resulting in less gastric acid secretion, causes the stomach lining to generate more much inhibits neutrophil activation thus

preventing injury from inflammation, and blocks the attachment of *Helicobacter pylori* to gastric cells.

### INDICATIONS

- Gastric ulcers, duodenal ulcers and stomach ulcers.
- Gastric mucosal lesions (erosion, haemorrhage, redness or edema) associated with Acute gastritis and acute exacerbation of chronic gastritis.
- Preanesthetic medication.

### ADVERSE REACTION:

- Constipation
- Diarrhoea
- Nausea
- Vomiting
- Dizziness

### DOSAGE AND ADMINISTRATION

- **Gastric ulcers, duodenal ulcers and stomach ulcers**

For adults, the usual dosage is 10mg as lafutidine orally administered twice a day, once after breakfast and once after the evening meal or before sleeping. The dose may be adjusted according to the patient's age and symptoms.

- **Gastric mucosal lesions (erosion, haemorrhage, redness or edema) associated with acute gastritis and acute exacerbation of chronic gastritis**

For adults, the usual dosage is 10mg as lafutidine orally administered once a day, once after the evening meal or before sleeping. The dose may be adjusted according to the patient's age and symptoms.

- **Preanesthetic Medication**

For adults, the usual dosage is 10mg as lafutidine orally administered twice, once before sleeping on the day before operation and once 2 hours before introduction of anesthetic on the day of operation.

**Important Precaution**

Patients should be carefully observed during treatment, and the minimum required dose should be used according to symptoms. If response is not evident, other treatments should be implemented. Careful observation should be made for any changes in haematological, hepatic or renal parameters, and for changes in other factors.

**Precautions Related to Dosage and Administration**

- In dialysis patients (not during dialysis), it is reported that their maximum blood concentration of lafutidine increase twice as high as that of normal adults.
- Therefore, the administration should be started carefully with lower dosage.

# **CHAPTER VII**

## **EXCIPIENT PROFILE**

## CHAPTER VII

### EXCIPIENT PROFILE

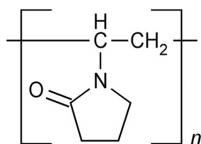
#### CROSPVIDONE

**Synonyms:**

- Cross linked povidone
- Kollido
- Polyplasdone
- Polyvinylpolypyrrolidone
- 1-vinyl-2pyrrolidione homopolymer

**Chemical name :**

- 1-Ethynyl-2-pyrrolidinone homopolymer

**Chemical structure****Empirical formula**

- $(C_6H_9NO)_n$

**Molecular Weight**

- >1,000 000

**Functional category**

- Tablet disintegrant

**Application in Pharmaceutical formulation**

- Tablet disintegrant and dissolution agent
- Solubility enhancer for poorly soluble drug

**Properties**

Acidity / Alkalinity	:	pH = 5.0 – 8.0 (1% w/v aqueous slurry)
Density	:	1.22 g/cm <sup>3</sup>
Density (bulk)	:	0.3-0.4 g/cm <sup>3</sup>
Density (tapped)	:	0.4-0.5 g/cm <sup>3</sup>
Moisture content	:	60%
Solubility	:	Practically insoluble in water

**Description**

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odourless or nearly odourless, hygroscopic powder.

**Stability and storage condition**

Crospovidone is hygroscopic; it should be stored in an airtight container in a cool, dry place

**Incompatibilities**

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adduct with some materials.

**Handling precautions:**

Observe normal precautions appropriate to the circumstances and quantity of materials handled. Eye protection, gloves, and a dust mask are

recommended (Handbook of Pharmaceutical excipients by Raymond C Rowe 5<sup>th</sup> edition, 214-216, MalahahBinti Mohamed et al., 2012).

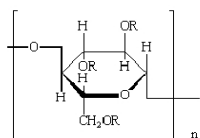
### Sodium Carboxy methyl Cellulose

**Synonyms** :- sodium cellulose glycolate, Na CMC, CMC, cellulose gum, sodium CMC; INS NO.466

**Chemical Names** :- Sodium salt of carboxymethyl ether of Cellulose.

**C.A.S. number** :- 9004-32-4

**Structural formula** :-



**Description**:-

white or slightly yellowish, almost odourless Hygroscopic granules, powder or fine fibres Agent Characteristics Identification

**Solubility (vol.4)** :-

Yield viscous colloidal solution with water ; insoluble In ethanol PURITY

**Loss on drying(vol.4)** :-

Not more than 12% after drying (105, to constant Weight).

**PH(vol.4)**:- 6.0-8.5(1 in 100 soln)

**Free glycolate** :-

Not more than 0.4% calculated as sodium glycolate on the dried basis

**Degree of substitution** :-

Not less than 0.20 and not more than 1.50



## Pregelatinized Starch

### Synonyms

- Compressible starch
- Instastarch
- Lycatab
- Lycatab
- Merigel
- Pharma –Gel
- Prejel
- Sepistab ST
- Starch 1500

### Chemical Name

- Pregelatinized Starch

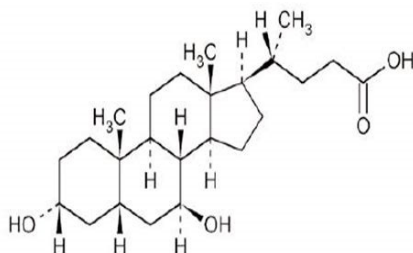
### Empirical Formula

- $(C_6H_{10}O_5)_n$

### Molecular Weight

- 300-1000

### Structural Formula



**Functional category**

- Tablet capsule diluents
- Capsule disintegrant
- Tablet binder

**Applications**

- Binder
- Diluent
- Disintegrant
- Lubricant

Use	Concentration %
Diluent (hard gelatine capsules)	5-75
Tablet Binder (Direct compression)	5-20
Tablet binder (wet granulation)	5-10
Tablet disintegrants	5-10

**Description**

- Pregelatinized starch occurs as a moderately coarse to fine, white to off-white coloured powder. It is odourless and has a slight characteristic taste.
- Pregelatinized starch contains 5% of free amylase, 15% of free amylopectin, and 80% unmodified starch.

**Properties**

Acidity / alkalinity	:	pH=4.5-7.0 for a 10% w/v aqueous dispersion
Angle of repose	:	40.7°
Density (Bulk)	:	0.586g/cm <sup>3</sup>
Density (tapped)	:	0.879g/cm <sup>3</sup>
Density (true)	:	1.516 g/cm <sup>3</sup>
Flowability	:	18-23 % (Compressibility index)
Moisture content	:	Pregelatinized maize starch is hygroscopic
Particle size distribution	:	30-150µm
Solubility	:	Practically insoluble in organic solvents.  Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Cold-water-soluble matter for partially pregelatinized starch is 10-20%.
Specific surface area	:	0.26m <sup>2</sup> /g
Viscosity (dynamic)	:	8-10 cP

**Safety:**

- Pregelatinized starch are widely used in oral dosage formulations. Prefelatinized starch is generally regarded as a nontoxic and non irritant excipient. However, oral consumption of large amounts of pregelatinized starch may be harmful.

**Handling precautions**

- Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

**Related substances:**

- Starch; starch, sterilizable maize

**Comments**

- A low moisture grade of pregelatinized starch, starch 1500 LM (Colorcon), containing less than 7% of water, specifically intended for use as a diluent in capsule formulations is commercially available.

**Magnesium Stearate****SYNONYMS**

Magnesium Octadecanoate

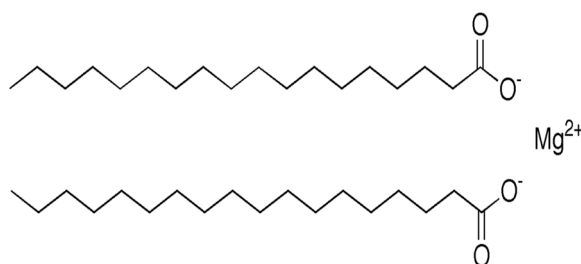
- Octadecanoic acid
- Magnesium salt
- Stearic acid
- Magnesium salt

**Chemical name and CAS Registry Number**

- Octadecnoic acid magnesium salt [(557-04-0)]

**Empirical formula and Molecular Weight**

- Magnesium stearate as a compound of a magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate.
- Magnesium stearate :  $C_{36}H_{72}MgO_4$
- Magnesium palmitate :  $C_{32}H_{64}MgO_4$
- Structural Formula :  $[CH_3(CH_2)_{16}COO]Mg$

**Functional category**

Tablet and capsule lubricant

**Applications in pharmaceutical formulations or technology**

- It is widely used in cosmetics, foods, and pharmaceutical formulations
- It is used as a lubricant in capsule and tablet manufacture at concentrations 0.25% and 5.0% w/w

**Description**

- Magnesium stearate is a very fine, light, white, precipitated or milled, impalpable powder of low density, having a faint odour of stearic acid and a characteristic taste
- The powder is greasy to the touch and readily adheres to the skin

**Properties**

Crystalline forms	:	High-purity magnesium stearate has been isolated as a trihydrate, adehydrate and anhydrate.
Density (bulk)	:	1.059g/cm <sup>3</sup>
Density (tapped)	:	0.286g/cm <sup>3</sup>
Density (true)	:	1.092g/cm <sup>3</sup>
Flash point	:	250°C
Flow ability	:	poorly flowing, cohesive powder
Melting range	:	117-150°C
(Commercial samples)	:	126-130°C (high purity magnesium stearate)
Solubility	:	practically insoluble in water; slightly soluble in warm benzene and warm ethanol (95%)
Specific surface area	:	1.6-14.8m <sup>2</sup> /g

**Stability and Storage Condition**

- Magnesium stearate is stable and should be stored in a well closed contained in a cool, dry place.

**Incompatibilities**

- Incompatible with strong acids, alkalis, and iron salts
- Magnesium stearate cannot be used containing aspirin, some vitamins, and most alkaloidal salts.

**Method of manufacture:**

- Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide, or carbonate with stearic acid at elevated temperatures.

**Safety**

- Magnesium stearate is widely used a pharmaceutical excipient and is generally regarded as being nontoxic as being nontoxic following oral following.
- However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

**Handling precautions**

- Eye protection and gloves are recommended
- Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking

**Related substances**

- Calcium stearate
- Magnesium aluminium silicate
- Stearic acid
- Zinc stearate

(Hand book of pharmaceutical excipients by Raymond C Rowe-5<sup>th</sup> editions, 430-435)

**MANNITOL****Synonyms:**

- Cordycepic acid
- Manna Sugar
- D-mannite
- Mannogrm
- Pearlitol

**Chemical Name :**

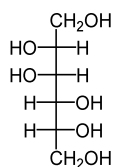
D-Mannitol

**Empirical formula**

$C_6H_{14}O_6$

**Molecular Weight**

182.17

**Structural Formula****Functional Category**

- Diluents
- Sweetening agent
- Tonicity agent



**Application**

- It is used as diluent in tablet formulations (10-90% w/w).
- It is used in pharmaceutical formulations and food products.
- It is used in tablet applications include antacid preparations glyceryltrinitrite tablets, and vitamin preparation
- It is used as an excipient in the manufacture of chewable tablet formulations
- Because of its negative heat of solution, sweetness, and mouth feel
- In lyophilized preparation, mannitol (20-90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plus in a vial
- It is used in food applications as a bulking agent
- Mannitol administered parentally is used as an osmotic diuretic; it is used in diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure.

**Description**

- Mannitol occurs as a white, odourless, crystalline powder, or free-flowing granules
- It has a sweet taste, approximately as sweet glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth.

**Properties****Density (bulk)**

- 0.430g/cm<sup>3</sup> for powder
- 0.7g/cm<sup>3</sup> for granule

**Density (tapped)**

- 0.734g/cm<sup>3</sup> for powder
- 0.8g/cm<sup>3</sup> for granules

**Melting point**

166-168°C

**Flash point**

<150°C

**Flow ability**

Powder is cohesive, granules are free flowing

**Specific surface area**

0.37-0.39m<sup>2</sup>/g

**Stability and storage conditions**

- Mannitol is stable in the dry state and in aqueous solutions
- The bulk material should be stored in a well-closed container in a cool, dry place

**Incompatibilities**

- Mannitol is incompatible with xylitol infusion and may form complex with some metals such as aluminium, copper, and iron
- Mannitol solutions, 20 % w/v or stronger, may be salted out by potassium chloride or sodium chloride.
- Mannitol reducing sugar impurities have been implicated in the oxidative degradation of a peptide in lyophilized formulation
- Mannitol was found to reduce the oral bioavailability of cimetidine compared to sucrose

**Handling precautions**

Mannitol may be irritant to the eyes; eye protection is recommended

**Related substances**

Sorbitol

**Microcrystalline Cellulose****Synonyms**

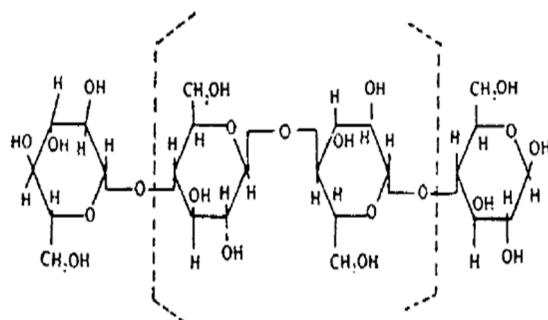
- Avicel pH
- Celex
- Celphere
- Ceolus KG
- Ethispheres
- Fibrocel
- Pharmacel
- Vivapur

**Chemical name**

Cellulose

**Empirical Formula**

$(C_6H_{10}O_5)_n$

**Structural formula :-****Molecular Weight**

36000

**Functional Category**

- Adsorbent
- Suspending agent
- Tablet and capsule diluents
- Tablet disintegrant

**Application in Pharmaceutical Formulation**

- Microcrystalline cellulose is used as a binder / diluent in oral tablet and capsule formulations
- Microcrystalline cellulose is used as a lubricant and disintegrant agent in tablet formulation
- Microcrystalline cellulose is also used in cosmetics and food products

**Description**

- Microcrystalline cellulose is a white, odourless, tasteless, crystalline powder composed of porous particles

- Microcrystalline cellulose is hygroscopic

**Use Concentration (%)**

Adsorbent	-	20-90
Anti-adherent	-	5-20
Capsule binder/diluents	-	20-90
Tablet disintegrants	-	5-15
Tablet binder/diluents	-	20-90

**Pharmacopoeial Specifications**

pH	-	5.0-7.0
Loss on drying	-	47.0 %
Residue on ignition	-	40.05%
Sulphated ash	-	40.1%
Heavy metals	-	410 ppm

**Typical properties**

Density (tapped)	-	0.478g/cm <sup>3</sup>
Density (True)	-	1.512-1.668g/cm <sup>3</sup>
Flowability	-	1.41g/s for Emcocel 90M
Melting point	-	hars at 260-2708C.

**Stability and Storage Conditions**

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well – closed container in a cool, dry place.

**Incompatibilities**

Microcrystalline cellulose is incompatible with strong oxidizing agents

**Handling precautions**

Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and adjust mask are recommended. (Hand book of Pharmaceutical excipients by Raymond C Rowe – 5<sup>th</sup> edition 132-135).

## **LACTOSE**

**1) Synonyms:**

- BP: Lactose monohydrate
- JP: Lactose

**2) Empirical formula:****3) Functional Formula:**

- Binding agent
- Diluent for dry-powder inhalers
- Tablet binder

**4) Application:**

- Lactose is widely used as a filler or diluents in tablets and capsules and to a more limited extent in lyophilized products and infant formulas.
- Lactose is also used a diluents in dry-powder inhalation.

- Direct compression grades of lactose are available as granulated / agglomerated  $\alpha$ -lactose monohydrate containing small amounts of anhydrous lactose.

**5) Typical properties:**

Compression pressure – 18.95-19.10 K N /cm<sup>2</sup>.

**6) Density:**

1.54 gm/cm<sup>3</sup>.

**7) Moisture content:**

Lactose monohydrate contains approximately 5% w/w water of crystallization and normally has an average of 4.5- 5.5%w/w water content.

## ASPARTAME

**Synonyms :-**

- ❖ Aspartyl Phenylalanine Methyl Ester  $\beta\beta$
- ❖ Nutra sweet
- ❖ Pat sweet
- ❖ Canderel
- ❖ Equal
- ❖ Pal sweet diet

**Chemical Name :-**

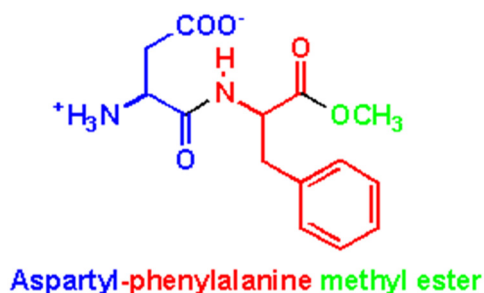
N-A-L-Aspartyl-L-Phenylalanine 1 -methyl ester

**Empirical Formula :-**

C<sub>14</sub> H<sub>18</sub> N<sub>2</sub>O<sub>5</sub>

**Molecular Weight :-**

294.31

**Structural Formula :-****Functional category :-**

Sweetering agent .

**Description :-**

Aspartame occurs as an off white, almost odourless, crystalline powder with an intensely sweet taste.

**Melting Point :-**

246-247°C

**Solubility :-**

Slightly soluble in ethanol (95 %); sparingly soluble in water. At 20 °C the solubility is 1% at acidic pH, e.g., at pH 2 and at 20°C solubility is 10% w/v.

**Solubility and Storage Conditions :-**

- Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl-L-phenylalanine & 3-benzoyl-6-carboxy-methyl-1,5-diketopiperazine. A third degradation product is also known, β-L-aspartyl-L-phenylalanine methyl ester.



- Aspartame degradation also occurs during prolonged heat treatment. Losse of aspartame may be minimized by using processes that employ high temperatures for a short time followed by rapid cooling.
- The bulk material should be stored in a well-closed container in a cool, dry place.



**SAFETY :-**

Aspartame is widely used in oral pharmaceutical formulation beverages; and food products as an intense sweetens and is generally regarded as a non – toxic material. The WHO has set an acceptable daily intake for aspartame at to 40 mg/kg body – weight.

**Handling precautions :-**

Observe normal precautions appropriate to the circumstances & quality of material handled. Measures should be taken to minimize the potential for dust explosion. Eye protection is recommended.

**Application :-**

-  Intense sweetening agent in beverage products, food products & table top sweetners, and in pharmaceutical preparations including tablets, powder mixs and vitamin preparations.
-  Therapeutically, aspartame has also been used in the treatment of sickle cell anemia.

## TALC

### Synonyms

- Altalc
- Hydrous magnesium calcium silicate
- Hydrous magnesium silicate

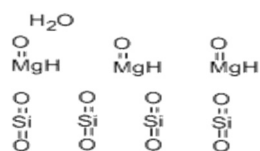
### Chemical Name

- Talc
- Purified talc
- Talcum

### Empirical Formula

- Talc is purified, hydrated, magnesium silicate
- $\text{Mg}_6(\text{Si}_2\text{O}_5)_4(\text{OH})_4$
- It may contain small, variable amounts silicate and iron

### Structural formula:-



### Functional category

- Anticaking agent
- Glidant
- Diluent

### Applications in Pharmaceutical formulation

- Talc is widely used in solid dosage formulation

- Diluents tablet and capsule (5.0-30.0)
- It is widely used as a dissolution retardant in the development of controlled – release products
- Talc is a novel powder coating for extended-release pellets, and as an adsorbent
- It is used as a dusting powder
- It is used to clarify liquids and is used in cosmetics and food products
- It is used to baby powder

### Description

Talc is a very fine, white to greyish-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft the touch and free from grittiness.

### Properties

- Acidity / alkalinity : pH=7-10 for a 20% w/v aqueous dispersion
- Moisture content : Talc absorbs insignificant amounts of water at 25 C at relative humidity up to about 90%
- Particle size distribution : varies with the source and grade of material. Two typical grades are >99% through a 44um (#325 mesh).

- Solubility : practically insoluble in diluents acids and alkalis, organic solvents, and water
- Specific surface area : 2.41-2.42m<sup>2</sup>/

**Stability and storage conditions**

- Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour.
- It may be also be sterilized by exposure to ethylene oxide or gamma irradiation
- It may be also be sterilized by exposure to ethylene oxide or gamma irradiation
- Talc should be stored in a well closed container in a cool, dry place

**Incompatibilities**

Incompatible with quaternary ammonium compounds

**Handling precautions**

- Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis
- In the UK, the occupational exposure limit for talc is long-term (8 hour TWA). Eye protection, gloves, and a respirator are recommended

**Related substances**

- Bentonite
- Magnesium aluminium silicate
- Magnesium silicate
- Magnesium trisilicate

# CHAPTER VIII

## EXPERIMENTAL DETAILS

## CHAPTER VIII

### EXPRIMENTAL DETAILS

#### I. CONSTRUCTION OF LAFUTIDINE CALIBRATION CURVE WITH PHOSPHATE BUFFER pH 6.8

##### **Preparation of pH 6.8 phosphate buffer solution**

Take 50 ml of 0.2M Potassium Dihydrogen phosphate in a 200ml volumetric flask and add 22.4ml of 0.2M Sodium hydroxide solution, then the volume was made up to 200ml using distilled water.

##### **Preparation of 0.2M potassium dihydrogen phosphate**

27.218g of potassium dihydrogen phosphate was dissolved in distilled water and the volume was made up to 1000 using distilled water.

##### **Preparation of 0.2M sodium hydroxide**

8g of sodium hydroxide was dissolved in distilled water and made up to 1000ml with distilled water.

##### **a. Determination of $\lambda$ -max**

100mg of Lafutidine is taken in a 100ml volumetric flask and dissolved by using a small amount of phosphate buffer and made up to 100ml. This stock solution containing 1000 $\mu$ g/ml. This is further diluted into 10 $\mu$ g/ml. The resultant solution is scanned in the range of (200-400nm).

##### **b. Preparation of calibration curve**

From the above prepared stock solution, different concentrations (5 to 50 $\mu$ g/ml) solutions are prepared. The absorbance of these solutions are measured at  $\lambda$ max (283)nm by UV- spectrophotometer. A standard curve is plotted using concentration on X-axis and the absorbance obtained on Y-axis.

## II. COMPATABILITY STUDIES FOR DRUG AND EXCIPIENTS

Compatibility studies are carried out to confirm whether there are no interactions existing between the drug and excipients. It gives information needed for selection of excipients with the drug for the formulation. Infrared spectroscopy and Differential scanning calorimetry studies are the two techniques used to check the compatibility between drug and polymers.

### **Fourier Transform Infra-Red spectroscopic(FTIR) studies**

FT–IR spectra were recorded for lafutidine pure drug and pure drug with excipients using IR- spectrophotometer. The samples were prepared in KBr dish and scanned over 4000 to 400  $\text{cm}^{-1}$ .

### **b.Differential scanning calorimetry (DSC) for best formulation:**

Differential scanning calorimetry is used for screening. The specified samples is hermetically sealed aluminium pans at temperature 20°C/min nitrogen werepurgd at 50ml/min and 100ml/min through cooling unit (**Himansu Chopra et al., 2012**).

## III. PRECOMPRESSION EVALUATION OF POWDER BLEND

The goals of the preformulation study are

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine its kinetics release rate profile.
- To establish its compatibility with different excipients.

**a. ANGLE OF REPOSE:**

The friction forces in a loose powder can be measured by the angle of repose ( $\theta$ ). It is an indicative of the flow properties of the powder. It is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\text{Angle of repose } (\theta) = \tan^{-1} \frac{h}{r}$$

Where,

- $\theta$  - angle of repose
- $h$  - height of pile in cm
- $r$  - radius of pile in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height ( $h$ ). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property (**Debjit Bhowmik et al., 2009**).

**TABLE 1: LIMITS FOR ANGLE OF REPOSE**

ANGLE OF REPOSE	POWDER FLOW
< 25 <sup>0</sup>	EXCELLENT
25-30 <sup>0</sup>	GOOD
30-40 <sup>0</sup>	PASSABLE
>40 <sup>0</sup>	VERY POOR



**b. Bulk Density (Db):**

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by **(Debjit Bhowmik et al., 2009)**.

$$\text{Bulk density} = \frac{\text{mass (m)}}{\text{bulk volume (Vb)}}$$

Where,

M - Mass of the Powder

Vb - Bulk volume of the powder

**c. TAPPED DENSITY:**

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume were noted if the difference between these two volumes is less than 2%. If it is more than 2%, then tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by **(Debjit Bhowmik et al., 2009)**

$$\text{Tapped density} = \frac{\text{mass (m)}}{\text{tapped volume (Vt)}}$$

Where,

M - mass of powder

Vt - tapped volume of the powder.

*D. PERCENTAGE OF COMPRESSIBILITY (OR) CARR'S INDEX:*

It indicates powder flow properties. It is expressed in percentage and is given as the Following

$$\text{Compressibility index} = \frac{\text{tapped density} - \text{bulk density} \times 100}{\text{tapped density}}$$

**TABLE 2:****RELATIONSHIP BETWEEN % COMPRESSIBILITY AND FLOW ABILITY**

% Compressibility	Flow ability
5 – 12	Excellent
12 – 16	Good
18 – 21	Fair passable
23 – 35	Poor
33 – 38	Very poor
< 40	Very very poor

**e.Hausner ratio:**

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula (**Debjit Bhowmik et al., 2009**).

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

**TABLE 3:**  
**Relationship between flow characters and Hausner's ratio**

Flow characters	Hausner's ratio
Excellent	1.00 – 1.11
Good	1.1 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 – 1.45
Very poor	1.46 – 1.59
Very very poor	>1.60

### III.FORMULATION OF LAFUTIDINE ORO-DISPERSIBLE TABLETS

#### Using different superdisintegrants

➤ **Synthetic superdisintegrants**

-Sodium Carboxy methyl cellulose

-Crospovidone

➤ **Natural superdisintegrants**

Pregelatinized starch

#### PREPARATION OF ORODISPERSIBLE TABLETS OF LAFUTIDINE

Lafutidine is mixed with super disintegrate crospovidone, sodium carboxy methyl cellulose, pregelatinize starch manitol used as mouth feel enhancer, Microcrysstalline cellulose as diluted and binder, lactose as diluents, aspartame as sweetner, talc as glidant and Magnesium stearte as lubricant. All the ingredients were passed through 60 mesh Separately, weighed and mixed

in geometrical order in to motor and pestle for 10 min.The blend thus obtained was directly compressed on 12 station rotary punching machine to get 10 mg of lafutidine.Each tablet weighing of 200 mg.

F1,F2,F3 formulation are prepared by using sodium carboxy methyl cellulose super disintegrants in 2%,3%,4% respectively.F4,F5,F6 frmulation prepared by using cros povidone superdisintegrant in 2%,3%,4% respectively.F7,F8,F9 formulation prepared by using pregelatinized starch superdisintegrants in 2%,3%,4% respectively.

F10.F11,F12 formulation prepared by using combination of SEMC ,pregelatinized starch, cros povidone in 3%,4.5%,12% respectively.

### **By direct compression**

All the formulation components other than lubricants and Glidant were accurately weighed, passed through 60-mesh sieve and mixed well for 30 min. Talc and magnesium stearate were passed through 80-mesh sieve, mixed with above blend for 10 min and resultant blend was directly compressed into tablets. The amount of all tablet components other than superdisintegrant and diluents were kept constant. Round flat tablets of 200 mg weight and 8 mm diameter were prepared using 12 station B/D tolling compression machine by direct compression technique.(**kalyankar et al., 2015**).

#### IV. EVALUATION OF POST COMPRESSION PARAMETERS OF LAFUTIDINE ORO-DISPERSIBLE TABLETS

##### a. General appearance

The general appearance of a tablet, its visual identity and over all “elegance” is essential for consumer acceptance. Tablet’s size, shape, colour, surface texture, physical flaws and consistency are noted.

##### ***B. TABLET THICKNESS & DIAMETER:***

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness and diameter can be measured using a simple procedure. 3 tablets were taken and their thickness and diameter was measured using digital Vernier calipers. **(Amit Modi *et al.*, 2012).**

##### ***C. TABLET HARDNESS:***

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Pfizer hardness tester **(Mukesh *et al.*, 2008).**

##### ***d. UNIFORMITY OF WEIGHT:***

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity **(Mukesh *et al.*, 2008).**

TABLE 3: I.

**P. SPECIFICATION FOR UNIFORMITY OF WEIGHT**

AVERAGE WEIGHT OF TABLET	% DEVIATION
80mg or Less	± 10
More than 80mg but less than 250mg	± 7.5
250mg or more	± 5

**e.Friability**

It is measure of mechanical strength of tablets. Roche Friabilator was used to determine the friability by following procedure. A preweighed tablet was placed in the Friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the Friabilator for at least 4 minutes. At the end of test tablets they were disused and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as **(Mukesh et al., 2008)**

$$\% \text{ FRIABILITY} = \text{LOSS IN WEIGHT} / \text{INITIAL WEIGHT} \times 100$$

$$\% \text{ friability} = \frac{w_0 - w_f}{w_0} \times 100$$

**f.Uniformity of drug content:**

Randomly Ten tablets of formulation were weighed and crushed in mortar and powder equivalent to lafutidine 200mg of lafutidine was weighed and dissolved in phosphate buffer pH 6.8, the volume was made up to 100ml. From the stock solution 10ml sample was withdrawn and diluted to 100ml with phosphate buffer Ph 6.8. The absorbance was measured at wavelength 283

nm using UV-Visible spectrophotometer. Content uniformity was calculated using formula (**Amit Modi et al., 2012**).

#### **g. *In vitro* dissolution studies**

Dissolution rate was studied by using USP type –II apparatus (dissolution test apparatus at 50 rpm) using 500 ml phosphate buffer pH 6.8 as dissolution medium. Temperature of the dissolution medium was maintained at  $37 \pm 0.5^{\circ}\text{C}$ , sample was withdrawn at every 5 min interval and diluted suitably and the absorbance of solution was measured by UV spectrophotometer method at 283nm and concentration of the drug is determined from the standard calibration.

#### **h. *In vitro* release studies details:**

Apparatus used	: USPXXIII dissolution test apparatus
Dissolution medium	: phosphate buffer pH 6.8
Dissolution medium volume	: 500ml
Temperature	: $37 \pm 0.5^{\circ}\text{C}$
Speed of paddle	: 50rpm
Sampling intervals	: 5 min
Sample withdraw	: 10ml
Absorbance measured	: 231nm

#### **i. *In vitro* disintegration time**

The test was carried out on 6 tablets using the apparatus specified in IP 2010 distilled water at  $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$  was used as a disintegration medium and the time in seconds taken for the entire tablet to disintegrate completely (**Shallesh Sharma et al., 2008**).

**DISINTEGRATION TIME**

- Uncoated tablets : 5 -30 minutes
- Coated tablets : 1- 2 hours
- Fast dissolving tablets : less than 3 minutes (European pharmacopeia)

**J. WATER ABSORPTION RATIO**

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and time required for complete wetting was measured. Three tablets from each formulation were prepared and standard deviation was also determined (**Venkateswara et al., 2014**).

The wetted tablet was then weighed. Water absorption ratio R, was determined using equation-

$$R = 100 \times (W_A - W_B) / W_B$$

Where,

W<sub>b</sub> = weight of the tablet before water absorption

W<sub>a</sub> = weight of the tablets after water absorption

**K. WETTING TIME**

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water or eosin dye and a tablet was put on the paper. The time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined (**venkateswara et al., 2014**).

**BEST FORMULATION SELECTION**

The selection of best formulation is done based on rate of Lafutidine release from the *in vitro* dissolution studied.



## **CHAPTER IX**

## **RESULT AND DISCUSSION**

## CHAPTER IX

### RESULTS AND DISCUSSION

#### I. PREPARATION OF STANDARD CALIBRATION CURVE FOR LAFUTIDINE

##### Determination of $\lambda$ -max

The absorption maximum ( $\lambda_{\text{max}}$  283 nm) of the Lafutidine was estimated by scanning the drug solution (10 $\mu$ g/ml) between 200-400 nm regions on UV spectrophotometer. The obtained spectrum showed that the absorption maximum ( $\lambda_{\text{max}}$ ) was 283 nm for the Lafutidine. **FIG.1**

##### Calibration of Lafutidine in phosphate buffer pH 6.8

The Standard Calibration curves of Lafutidine were prepared using phosphate buffer pH 6.8. The absorbance were measured at  $\lambda_{\text{max}}$  of 283nm. The correlation coefficient was found to be 0.9994. Lafutidine obeys the beer's law within the concentration range of (5-50 $\mu$ g/ml). Calibration plot of lafutidine in phosphate buffer pH 6.8 was shown in **FIG.2 and Table 1**.

#### II. COMPATABILITY STUDIES FOR DRUG AND EXCIPIENTS

##### Fourier Transform Infra-Red Spectroscopic (FT-IR) Studies

FT-IR spectrum of the pure drug and mixture of pure drug and excipients used in the formulation were recorded. The spectra of pure Lafutidine showed characteristic peaks at 3282  $\text{cm}^{-1}$ , 3118 $\text{cm}^{-1}$ , 1656  $\text{cm}^{-1}$ , 1608 $\text{cm}^{-1}$ . All the above peaks were also observed in the spectra of mixture of lafutidine and excipients with slight deviations. This indicating that the drug is stable and there is no drug-excipient interaction (**Bhaskar Umarji et al., 2012**) **Fig. 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H and 3I** .

### III. PREFORMULATION EVALUATION OF POWDER BLEND

The prepared tablets were evaluated on various parameters such as thickness and diameter, hardness, weight variation, friability, uniformity content, wetting time, water absorption ratio, *In-vitro* disintegration time and *In-vitro* dissolution test. The results were summarized in **Table 3**.

#### **Angle of repose**

The angle of repose was used to determine the flow properties of powder blend. The angle of repose of the formulations ranged from 24° 05' to 30° 02'. The results indicated that the formulations with synthetic superdisintegrants exhibited good flow properties whereas the natural superdisintegrants had a passable flow property. The results of angle of repose for all the formulations were shown in **Table 3** and **FIG. 6**.

#### **Bulk density**

The bulk density is used as an index of the ability of the powder to flow. The bulk density of the formulations was in the range of 0.684 – 0.711 g/ml. The values of bulk density showed that the blend was not tightly packed and indicated good flow properties for synthetic super disintegrants and passable for natural super disintegrants diluents. The results of bulk density for all the formulations were shown in **Table 3** and **FIG. 7**.

#### **Tapped density**

The tapped density was used to access the free flowing properties of powder blend. The tapped density of the formulations were in the range of 0.77- 0.87 g/cm<sup>3</sup>. The results indicated that the blends of the formulation had good flow properties for synthetic superdisintegrants and passable for natural

superdisintegrants. The results of tapped density for all the formulations were shown in **Table 3** and **FIG. 8**.

#### **Carr's compressibility index**

The Carr's compressibility index was used to access the free flowing properties of powder blend. The compressibility index of all the formulations ranged from 16.9 –23.17%. The value below 16% has a good flow property and good propensity of compression. The results of compressibility for all formulations were shown in **Table 3** and **FIG. 9**.

#### **Hausner's ratio**

The Hausner's ratio was an indirect index of ease of powder flow. The Hausner's ratio of all the formulations ranged from 1.11-1.25. This indicates better flow property of blend. The results of Hausner's ratio for all the formulations were shown in **Table 3** and **FIG.10**.

### **IV. FORMULATION OF LAFUTIDINE ORODISPERSIBLE TABLETS**

The orodispersible tablets of Lafutidine was prepared by direct compression method using synthetic superdisintegrants (sodium carboxy methyl cellulose and crospovidone) and natural superdisintegrants (pre gelatinized starch). The compositions of the different formulation were given in **Table 2A and 2B**. Twelve Formulations (F1 to F12) were prepared as per formula designed. All the tablets were white color and round in shape having 6 mm diameter.

### **V. POST COPMRESSION EVALUATION**

#### **a. General appearance**

The tablets were white coloured and round shaped. All tablets were elegant in appearance.

**b. Thickness and diameter**

The thickness and diameter of the formulations were used to determine the uniformity of size and shape of the tablets. From the results it was found that the thickness of the tablet in all formulation was 3.3-3.4mm and the diameter of the tablet in all formulation was 6mm. The results indicated that all the formulations had uniform size and shape. The results were shown in **Table 4A**.

**c. Hardness**

The hardness of the tablets was used to determine the resistance capacity of the tablets to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage. The hardness of the tablets of all the formulations was found to be in the range of 3.16-3.76 kg/cm<sup>2</sup>. The result indicated that all the tablets had a good mechanical strength. The results of the hardness for all the formulations were shown in **Table 4A**.

**d. Weight variation test**

The weight variation test was used to ensure the uniformity of the tablet in all formulations. The weight of all the tablets from each formulation was in the range from 193.4 mg to 200.70 mg. It was found all the tablets passed weight variation test, as the percentage weight variation was within the acceptable limits of  $\pm 7.5\%$ . The results were shown in **Table 4A**.

**e. Friability test**

Friability test was measured to ensure the mechanical strength of tablet. The results showed that the friability of all the formulation ranged from 0.48% to 0.65%. Friability of all the formulation was lesser than 1 % which indicated

the tablets had a good mechanical resistance. The results were shown in **Table 4A**.

**f. Uniformity of drug content**

The uniformity content test was used to determine the uniform amount of active ingredient present in all formulations. The drug content in the content uniformity of all the formulations was found to be in the range of 98.2 % - 99.70%. The results indicated all the formulations were within the acceptable limits as per USP limits. The results were shown in **Table 4A**.

**g. *In vitro* drug release study**

The dissolution profile range in 30 minutes was 88.13% to 97.79% (Table 5A and 5B). The drug release was found to be comparatively less in formulation containing natural superdisintegrant (pre gelatinized starch). The maximum dissolution drug release rate was observed with the formulation containing scmc + crospovidone + pregelatinizedstarch as a synthetic superdisintegrants.(**FIG. 12A, 12B, 12C and 12D**)

The formulation containing scmc +crospovidone+pregelatinized starch (3%+ 4.5%+ 12%) was to show dissolution in 30minutes of dissolution study produced 97.79% which compiled with WHO guideline. Many factors contributed for faster drug release rate such as rapid disintegration and increased wettability. Among the 12 formulations the formulation 12 (F12) was selected, as a best formulation because of its desirable character of low disintegration time, highest drug release, high water absorption rate and short wetting time.

**h. *In vitro* disintegration time**

The *in-vitro* disintegration time was determined by disintegration test apparatus. The results were shown in **Table 4B**. Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11 and F12 showed the disintegration time

65.0, 50.06, 30.0, 70.6, 45.3, 32.3, 50.0, 40.0, 25.0, 25.6, 20.6 and 18.0 seconds respectively. It was observed that Formulation F12 containing scmc +crospovidone+pre gelatinized starch (3% + 4.5% + 12%) disintegrated rapidly in a short time (18.0 seconds). The results of disintegration of all the tablets were found to be lesser than 180 seconds. So all the formulation satisfied the criteria of fast dissolving tablets.

#### **i. Water absorption ratio**

The water absorption ratio test was used to ensure the capacity of the superdisintegrant and the diluent to absorb the water. The results of water absorption ratio of all the formulation were shown in **Table 4B**.

Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11 and F12 showed the water absorption ratio 75.18%, 71.28 %, 75.18%, 16.58%, 78.53, 85.72%, 71.53%, 71.53%, 96.64%, 81.65%, 94.11%, and 98.78% respectively. The results showed that as concentration of superdisintegrant increased water absorption ratio was also increased. Formulation F12 containing scmc +crospovidone+pre gelatinized starch (3% + 4.5% + 12%) as showed highest water absorption ratio (98.78%) when compared to other formulations.

The reason for high water absorption ratio for F12 formulation containing scmc +crospovidone + pre gelatinized starch quickly wicks water in to the tablet to generate volume expansion. scmc + crospovidone + pre gelatinized starch uses combination of swelling and wicking.

#### **j. Wetting time**

Wetting time of the tablet was used to assess the capacity of the tablets to disintegrate by swelling in water. All the formulations showed

quick wetting, this may be due to ability to swelling and also capacity of absorption of water. The results of wetting time of all the formulations were shown in **Table 4B**.

The formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11 and F12 showed the wetting time, 68.17, 62.0, 69.6, 72.6, 73.0, 70.9, 56.0, 65.9, 54.0, 56.0, 61.2 and 69.1 seconds respectively. The results indicated that the concentration of superdisintegrant influenced the wetting time. Formulation F12 containing scmc +crospovidone+pre gelatinized starch (3% + 4.5% + 12%) showed lesser wetting time than other formulations.

This may be due to fact that superdisintegrant – scmc +crospovidone+pre gelatinized starch performed its action by the combination of wicking and swelling action. Formulation F12 showed shorter wetting time. (Debjit Bhowmik *et al.*, 2009).

#### **VI. COMPARISON OF DISSOLUTION DATA OF LAFUTIDINE TABLETS CONTAINING DIFFERENT SUPERDISINTEGRANTS**

The tablets prepared with scmc +crospovidone+pre gelatinized starch showed maximum drug release of 97.79% whereas tablets containing sodium mannitol diluent showed maximum drug release of 92.38%, 94.05% and 97.79% respectively.

#### **VII. SELECTION OF BEST FORMULATION**

Among twelve formulations, the best was selected on the basis of lowest disintegration time, rapid drug release profile, higher water absorption ratio, short wetting time. Formulation F12 showed lowest disintegration time of 18.0 seconds, faster drug release rate of 97.79 % in



30 minutes, comparatively high water absorption ratio of 98.78% and short wetting time of 69.1 seconds. In these parameter would drive the F12 formulation as a best formulation.

### **VIII. EVALUATION OF SELECTED FORMULATION**

#### **a. Differential Scanning Calorimetry (DSC) Studies**

Any possible drug polymer interaction can be studied by thermal analysis. The DSC thermogram of lafutidine exhibited an sharp endothermic peak at at 104.18°C, which corresponding to its melting temperature. The thermogram of the final best formulation of lafutidine with other excipients show the existence of drug endothermic peak within the range which indicated the absence of interaction between the drug and other excipients. The DSC thermogram of pure drug and the final best formulation is presented in **FIG. 5A and 5B** .

#### **b. Fourier Transform Infra-Red (FT-IR) Spectroscopic studies**

Infrared spectra of the lafutidine orodispersible tablets showed major peaks at 3282 cm<sup>-1</sup>, 3118cm<sup>-1</sup>, 1656 cm<sup>-1</sup>, 1608cm<sup>-1</sup> indicated that there was no interaction between the drug and the final formulation throughout the preparation of orodispersible tablets. The result was shown in **FIG. 3J**.

**TABLE- 1 CALIBRATION OF LAFUTIDINE USING PHOSPHATE  
BUFFER PH<sup>6.8</sup>**

<b>S.NO</b>	<b>CONCENTRATION (µg/ml)</b>	<b>ABSORBANCE</b>
1	5	0.0843 ± 0.0019
2	10	0.1606 ± 0.0028
3	15	0.2427 ± 0.0044
4	20	0.3251 ± 0.0186
5	25	0.3982 ± 0.0104
6	30	0.4756 ± 0.0093
7	35	0.5542 ± 0.0135
8	40	0.6311 ± 0.0061
9	45	0.7123 ± 0.0168
10	50	0.7894 ± 0.0214

**Regression – 0.9994 ± 0.0001667**

**TABLE- 2 COMPOSITION OF ORODISPERSIBLE TABLE OF LAFUTIDINE**

S.NO	Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Lafutidine	10	10	10	10	10	10	10	10	10	10	10	10
2	Sodium carboxy methyl cellulose	5	10	15	-	-	-	-	-	-	-	-	-
3	Crospovidone	-	-	-	5	10	15	-	-	-	-	-	-
4	Pregelatinized Starch	-	-	-	-	-	-	5	10	15	-	-	-
5	Scmc + Cross + Press	-	-	-	-	-	-	-	-	-	10	15	20
6	Microcrystalline cellulose	90	90	90	90	90	90	90	90	90	90	90	90
7	Lactose	61	56	51	61	56	51	61	56	51	56	51	46
8	Mannitol	20	20	20	20	20	20	20	20	20	20	20	20
9	Aspartame	10	10	10	10	10	10	10	10	10	10	10	10
10	Talc	2	2	2	2	2	2	2	2	2	2	2	2
11	Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2

**TABLE 3 -EVALUATION OF MIXED POWDER BLEND OF LAFUTIDINE**

<b>Formulation Code</b>	<b>Angle of repose (°) ± SD*</b>	<b>Bulk density (g/ml) ± SD*</b>	<b>Tapped density (g/ml) ± SD*</b>	<b>Carrs index (%) ± SD*</b>	<b>Hausner's ratio ± SD*</b>	<b>Drug Content (%) ± SD*</b>
F1	28.1 ± 0.09	0.704 ± 0.07	0.775 ± 0.19	19.0 ± 0.01	1.10 ± 0.02	0.775 ± 0.19
F2	26.3 ± 0.12	0.684 ± 0.18	0.833 ± 0.31	17.9 ± 0.08	1.21 ± 0.03	0.833 ± 0.31
F3	27.34 ± 0.24	0.693 ± 0.65	0.806 ± 0.23	16.9 ± 0.03	1.16 ± 0.01	0.806 ± 0.23
F4	26.9 ± 0.10	0.687 ± 0.35	0.840 ± 0.24	18.17 ± 0.01	1.22 ± 0.03	0.840 ± 0.24
F5	30.0 ± 0.02	0.707 ± 0.17	0.848 ± 0.09	16.66 ± 0.54	1.20 ± 0.03	0.848 ± 0.09
F6	28.0 ± 0.03	0.685 ± 0.20	0.824 ± 0.28	21.5 ± 0.02	1.20 ± 0.01	0.824 ± 0.28
F7	24.05 ± 0.39	0.711 ± 0.12	0.790 ± 0.19	20.8 ± 0.02	1.11 ± 0.02	0.790 ± 0.19
F8	27.37 ± 0.24	0.70 ± 0.16	0.875 ± 0.41	23.1 ± 0.01	1.25 ± 0.01	0.875 ± 0.41
F9	25.75 ± 0.12	0.697 ± 0.35	0.776 ± 0.29	23.7 ± 0.01	1.11 ± 0.00	0.776 ± 0.29
F10	29.40 ± 0.41	0.70 ± 0.16	0.875 ± 0.41	22.8 ± 0.01	1.25 ± 0.02	0.875 ± 0.41
F11	28.61 ± 0.10	0.687 ± 0.35	0.840 ± 0.24	18.7 ± 0.02	1.22 ± 0.03	0.840 ± 0.24
F12	27.34 ± 0.29	0.693 ± 0.65	0.806 ± 0.23	16.9 ± 0.03	1.16 ± 0.01	0.806 ± 0.23

TABLE 4 - EVALUATION OF ORODISPERSIBLE TABLE OF LAFUTIDINE

Formulation Code	General appearance	Thickness mm	Hardness kg/m <sup>2</sup>	Average weight (mg) $\pm 7.5$	Friability (%)	Content uniformity	Disintegration Time (sec)	Water absorption ratio (%)	Wetting time (sec)
F1	white	3.56 $\pm$ 0.01	3.26 $\pm$ 0.15	200.0 $\pm$ 0.41	0.55 $\pm$ 0.51	99.55 $\pm$ 0.86	65.0 $\pm$ 1.63	75.18 $\pm$ 0.50	68.17 $\pm$ 0.27
F2	white	3.43 $\pm$ 0.01	3.43 $\pm$ 0.05	200.7 $\pm$ 0.62	0.48 $\pm$ 0.06	97.15 $\pm$ 0.95	50.6 $\pm$ 0.47	71.28 $\pm$ 1.69	62.0 $\pm$ 0.81
F3	white	3.42 $\pm$ 0.01	3.16 $\pm$ 0.40	199.56 $\pm$ 0.49	0.55 $\pm$ 0.02	89.06 $\pm$ 0.75	30.0 $\pm$ 1.63	75.18 $\pm$ 1.29	69.6 $\pm$ 1.2
F4	white	3.32 $\pm$ 0.11	3.50 $\pm$ 0.40	199.2 $\pm$ 0.18	0.65 $\pm$ 0.03	87.14 $\pm$ 0.95	70.6 $\pm$ 2.3	60.58 $\pm$ 1.11	72.6 $\pm$ 1.2
F5	white	3.39 $\pm$ 0.05	3.50 $\pm$ 0.40	204.6 $\pm$ 0.52	0.53 $\pm$ 0.16	85.78 $\pm$ 0.78	45.3 $\pm$ 1.70	78.53 $\pm$ 0.84	73.0 $\pm$ 0.8
F6	white	3.32 $\pm$ 0.00	3.00 $\pm$ 0.40	201.3 $\pm$ 0.63	0.60 $\pm$ 0.08	88.62 $\pm$ 0.40	32.3 $\pm$ 1.70	85.72 $\pm$ 0.43	70.9 $\pm$ 0.55
F7	white	3.42 $\pm$ 0.00	3.66 $\pm$ 0.84	202.6 $\pm$ 0.58	0.57 $\pm$ 0.16	90.24 $\pm$ 0.31	50.0 $\pm$ 1.63	71.53 $\pm$ 0.43	56.0 $\pm$ 1.6
F8	white	3.32 $\pm$ 0.00	3.33 $\pm$ 0.23	199.1 $\pm$ 0.53	0.59 $\pm$ 0.14	88.71 $\pm$ 0.31	40.0 $\pm$ 1.33	71.53 $\pm$ 1.07	65.9 $\pm$ 0.4
F9	white	3.39 $\pm$ 0.00	3.66 $\pm$ 0.84	193.4 $\pm$ 0.37	0.59 $\pm$ 0.01	88.94 $\pm$ 0.85	25.0 $\pm$ 1.47	96.64 $\pm$ 1.89	54.0 $\pm$ 1.6
F10	white	3.32 $\pm$ 0.00	3.66 $\pm$ 0.84	198.2 $\pm$ 0.19	0.52 $\pm$ 0.01	99.98 $\pm$ 0.72	25.6 $\pm$ 0.21	81.65 $\pm$ 1.78	56.0 $\pm$ 1.4
F11	white	3.43 $\pm$ 0.17	3.76 $\pm$ 0.40	199.0 $\pm$ 0.08	0.53 $\pm$ 0.068	99.17 $\pm$ 0.06	20.6 $\pm$ 0.96	94.11 $\pm$ 1.89	61.2 $\pm$ 0.23
F12	white	3.43 $\pm$ 0.05	3.16 $\pm$ 0.62	199.2 $\pm$ 0.48	0.55 $\pm$ 0.02	99.94 $\pm$ 0.06	18.0 $\pm$ 0.4	98.78 $\pm$ 1.89	69.1 $\pm$ 1.2

**Table 5 A - VITRO RELEASE PROFILE OF LUFUTIDINE ORODISPERSIBLE TABLETS**

Time in Minutes	Cumulative Percentage drug release $\pm$ SD*					
	F1	F2	F3	F4	F5	F6
5	41.75 $\pm$ 0.29	30.43 $\pm$ 0.86	32.35 $\pm$ 0.87	33.40 $\pm$ 0.29	26.42 $\pm$ 0.32	17.68 $\pm$ 1.04
10	54.45 $\pm$ 0.22	48.66 $\pm$ 1.49	59.58 $\pm$ 1.49	58.70 $\pm$ 0.18	37.85 $\pm$ 0.42	32.78 $\pm$ 0.45
15	62.49 $\pm$ 0.96	60.76 $\pm$ 2.16	65.28 $\pm$ 2.47	67.13 $\pm$ 0.41	50.58 $\pm$ 0.51	53.47 $\pm$ 1.13
20	79.35 $\pm$ 2.77	76.84 $\pm$ 2.72	76.76 $\pm$ 3.32	78.49 $\pm$ 0.29	67.44 $\pm$ 1.81	64.89 $\pm$ 1.19
25	77.39 $\pm$ 2.09	83.66 $\pm$ 1.53	85.62 $\pm$ 2.76	87.21 $\pm$ 0.44	72.84 $\pm$ 0.41	72.84 $\pm$ 0.41
30	87.13 $\pm$ 1.05	86.51 $\pm$ 0.52	94.44 $\pm$ 1.82	94.05 $\pm$ 0.47	90.20 $\pm$ 1.50	86.20 $\pm$ 1.50

**Table 5 B - VITRO RELEASE PROFILE OF LUFUTIDINE ORODISPERSIBLE TABLETS**

Time in Minutes	Cumulative Percentage drug release $\pm$ SD*					
	F7	F8	F9	F10	F11	F12
5	17.90 $\pm$ 1.04	33.40 $\pm$ 0.29	12.93 $\pm$ 0.23	31.65 $\pm$ 0.20	33.40 $\pm$ 40	59.22 $\pm$ 1.19
10	25.82 $\pm$ 0.45	58.70 $\pm$ 0.18	26.43 $\pm$ 0.54	51.42 $\pm$ 0.46	58.70 $\pm$ 0.18	80.31 $\pm$ 1.18
15	33.24 $\pm$ 1.13	67.13 $\pm$ 0.41	40.61 $\pm$ 0.94	65.89 $\pm$ 1.19	67.13 $\pm$ 0.41	89.67 $\pm$ 0.34
20	43.89 $\pm$ 1.19	78.49 $\pm$ 0.29	55.54 $\pm$ 1.47	76.21 $\pm$ 1.50	78.49 $\pm$ 0.29	91.12 $\pm$ 0.33
25	58.70 $\pm$ 0.41	87.21 $\pm$ 0.44	71.42 $\pm$ 4.61	83.21 $\pm$ 1.42	87.49 $\pm$ 0.44	95.49 $\pm$ 1.41
30	88.87 $\pm$ 1.50	94.05 $\pm$ 0.47	88.55 $\pm$ 1.19	92.38 $\pm$ 0.45	94.05 $\pm$ 0.47	97.79 $\pm$ 0.88

# **CHAPTER X**

## **TABLES AND FIGURES**



**TABLE- 1 CALIBRATION OF LAFUTIDINE USING PHOSPHATE  
BUFFER PH<sup>6.8</sup>**

<b>S.NO</b>	<b>CONCENTRATION (µg/ml)</b>	<b>ABSORBANCE</b>
1	5	0.0843 ± 0.0019
2	10	0.1606 ± 0.0028
3	15	0.2427 ± 0.0044
4	20	0.3251 ± 0.0186
5	25	0.3982 ± 0.0104
6	30	0.4756 ± 0.0093
7	35	0.5542 ± 0.0135
8	40	0.6311 ± 0.0061
9	45	0.7123 ± 0.0168
10	50	0.7894 ± 0.0214

**Regression – 0.9994 ± 0.0001667**

**TABLE- 2 COMPOSITION OF ORODISPERSIBLE TABLE OF LAFUTIDINE**

S.NO	Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Lafutidine	10	10	10	10	10	10	10	10	10	10	10	10
2	Sodium carboxy methyl cellulose	5	10	15	-	-	-	-	-	-	-	-	-
3	Crospovidone	-	-	-	5	10	15	-	-	-	-	-	-
4	Pregelatinized Starch	-	-	-	-	-	-	5	10	15	-	-	-
5	Scmc + Cross + Press	-	-	-	-	-	-	-	-	-	10	15	20
6	Microcrystalline cellulose	90	90	90	90	90	90	90	90	90	90	90	90
7	Lactose	61	56	51	61	56	51	61	56	51	56	51	46
8	Mannitol	20	20	20	20	20	20	20	20	20	20	20	20
9	Aspartame	10	10	10	10	10	10	10	10	10	10	10	10
10	Talc	2	2	2	2	2	2	2	2	2	2	2	2
11	Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2

**TABLE 3 -EVALUATION OF MIXED POWDER BLEND OF LAFUTIDINE**

<b>Formulation Code</b>	<b>Angle of repose (°) ± SD*</b>	<b>Bulk density (g/ml) ± SD*</b>	<b>Tapped density (g/ml) ± SD*</b>	<b>Carrs index (%) ± SD*</b>	<b>Hausner's ratio ± SD*</b>	<b>Drug Content (%) ± SD*</b>
F1	28.1 ± 0.09	0.704 ± 0.07	0.775 ± 0.19	19.0 ± 0.01	1.10 ± 0.02	0.775 ± 0.19
F2	26.3 ± 0.12	0.684 ± 0.18	0.833 ± 0.31	17.9 ± 0.08	1.21 ± 0.03	0.833 ± 0.31
F3	27.34 ± 0.24	0.693 ± 0.65	0.806 ± 0.23	16.9 ± 0.03	1.16 ± 0.01	0.806 ± 0.23
F4	26.9 ± 0.10	0.687 ± 0.35	0.840 ± 0.24	18.17 ± 0.01	1.22 ± 0.03	0.840 ± 0.24
F5	30.0 ± 0.02	0.707 ± 0.17	0.848 ± 0.09	16.66 ± 0.54	1.20 ± 0.03	0.848 ± 0.09
F6	28.0 ± 0.03	0.685 ± 0.20	0.824 ± 0.28	21.5 ± 0.02	1.20 ± 0.01	0.824 ± 0.28
F7	24.05 ± 0.39	0.711 ± 0.12	0.790 ± 0.19	20.8 ± 0.02	1.11 ± 0.02	0.790 ± 0.19
F8	27.37 ± 0.24	0.70 ± 0.16	0.875 ± 0.41	23.1 ± 0.01	1.25 ± 0.01	0.875 ± 0.41
F9	25.75 ± 0.12	0.697 ± 0.35	0.776 ± 0.29	23.7 ± 0.01	1.11 ± 0.00	0.776 ± 0.29
F10	29.40 ± 0.41	0.70 ± 0.16	0.875 ± 0.41	22.8 ± 0.01	1.25 ± 0.02	0.875 ± 0.41
F11	28.61 ± 0.10	0.687 ± 0.35	0.840 ± 0.24	18.7 ± 0.02	1.22 ± 0.03	0.840 ± 0.24
F12	27.34 ± 0.29	0.693 ± 0.65	0.806 ± 0.23	16.9 ± 0.03	1.16 ± 0.01	0.806 ± 0.23

TABLE 4 - EVALUATION OF ORODISPERSIBLE TABLE OF LAFUTIDINE

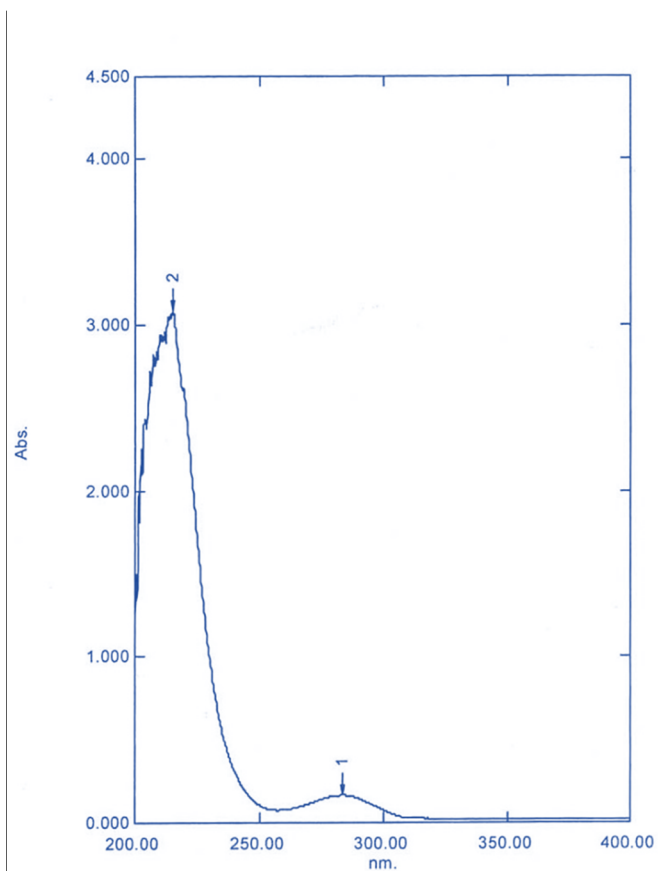
Formulation Code	General appearance	Thickness mm	Hardness kg/m <sup>2</sup>	Average weight (mg) $\pm$ 7.5	Friability (%)	Content uniformity	Disintegration Time (sec)	Water absorption ratio (%)	Wetting time (sec)
F1	white	3.56 $\pm$ 0.01	3.26 $\pm$ 0.15	200.0 $\pm$ 0.41	0.55 $\pm$ 0.51	99.55 $\pm$ 0.86	65.0 $\pm$ 1.63	75.18 $\pm$ 0.50	68.17 $\pm$ 0.27
F2	white	3.43 $\pm$ 0.01	3.43 $\pm$ 0.05	200.7 $\pm$ 0.62	0.48 $\pm$ 0.06	97.15 $\pm$ 0.95	50.6 $\pm$ 0.47	71.28 $\pm$ 1.69	62.0 $\pm$ 0.81
F3	white	3.42 $\pm$ 0.01	3.16 $\pm$ 0.40	199.56 $\pm$ 0.49	0.55 $\pm$ 0.02	89.06 $\pm$ 0.75	30.0 $\pm$ 1.63	75.18 $\pm$ 1.29	69.6 $\pm$ 1.2
F4	white	3.32 $\pm$ 0.11	3.50 $\pm$ 0.40	199.2 $\pm$ 0.18	0.65 $\pm$ 0.03	87.14 $\pm$ 0.95	70.6 $\pm$ 2.3	60.58 $\pm$ 1.11	72.6 $\pm$ 1.2
F5	white	3.39 $\pm$ 0.05	3.50 $\pm$ 0.40	204.6 $\pm$ 0.52	0.53 $\pm$ 0.16	85.78 $\pm$ 0.78	45.3 $\pm$ 1.70	78.53 $\pm$ 0.84	73.0 $\pm$ 0.8
F6	white	3.32 $\pm$ 0.00	3.00 $\pm$ 0.40	201.3 $\pm$ 0.63	0.60 $\pm$ 0.08	88.62 $\pm$ 0.40	32.3 $\pm$ 1.70	85.72 $\pm$ 0.43	70.9 $\pm$ 0.55
F7	white	3.42 $\pm$ 0.00	3.66 $\pm$ 0.84	202.6 $\pm$ 0.58	0.57 $\pm$ 0.16	90.24 $\pm$ 0.31	50.0 $\pm$ 1.63	71.53 $\pm$ 0.43	56.0 $\pm$ 1.6
F8	white	3.32 $\pm$ 0.00	3.33 $\pm$ 0.23	199.1 $\pm$ 0.53	0.59 $\pm$ 0.14	88.71 $\pm$ 0.31	40.0 $\pm$ 1.33	71.53 $\pm$ 1.07	65.9 $\pm$ 0.4
F9	white	3.39 $\pm$ 0.00	3.66 $\pm$ 0.84	193.4 $\pm$ 0.37	0.59 $\pm$ 0.01	88.94 $\pm$ 0.85	25.0 $\pm$ 1.47	96.64 $\pm$ 1.89	54.0 $\pm$ 1.6
F10	white	3.32 $\pm$ 0.00	3.66 $\pm$ 0.84	198.2 $\pm$ 0.19	0.52 $\pm$ 0.01	99.98 $\pm$ 0.72	25.6 $\pm$ 0.21	81.65 $\pm$ 1.78	56.0 $\pm$ 1.4
F11	white	3.43 $\pm$ 0.17	3.76 $\pm$ 0.40	199.0 $\pm$ 0.08	0.53 $\pm$ 0.068	99.17 $\pm$ 0.06	20.6 $\pm$ 0.96	94.11 $\pm$ 1.89	61.2 $\pm$ 0.23
F12	white	3.43 $\pm$ 0.05	3.16 $\pm$ 0.62	199.2 $\pm$ 0.48	0.55 $\pm$ 0.02	99.94 $\pm$ 0.06	18.0 $\pm$ 0.4	98.78 $\pm$ 1.89	69.1 $\pm$ 1.2

**Table 5 A - VITRO RELEASE PROFILE OF LUFUTIDINE ORODISPERSIBLE TABLETS**

Time in Minutes	Cumulative Percentage drug release $\pm$ SD*					
	F1	F2	F3	F4	F5	F6
5	41.75 $\pm$ 0.29	30.43 $\pm$ 0.86	32.35 $\pm$ 0.87	33.40 $\pm$ 0.29	26.42 $\pm$ 0.32	17.68 $\pm$ 1.04
10	54.45 $\pm$ 0.22	48.66 $\pm$ 1.49	59.58 $\pm$ 1.49	58.70 $\pm$ 0.18	37.85 $\pm$ 0.42	32.78 $\pm$ 0.45
15	62.49 $\pm$ 0.96	60.76 $\pm$ 2.16	65.28 $\pm$ 2.47	67.13 $\pm$ 0.41	50.58 $\pm$ 0.51	53.47 $\pm$ 1.13
20	79.35 $\pm$ 2.77	76.84 $\pm$ 2.72	76.76 $\pm$ 3.32	78.49 $\pm$ 0.29	67.44 $\pm$ 1.81	64.89 $\pm$ 1.19
25	77.39 $\pm$ 2.09	83.66 $\pm$ 1.53	85.62 $\pm$ 2.76	87.21 $\pm$ 0.44	72.84 $\pm$ 0.41	72.84 $\pm$ 0.41
30	87.13 $\pm$ 1.05	86.51 $\pm$ 0.52	94.44 $\pm$ 1.82	94.05 $\pm$ 0.47	90.20 $\pm$ 1.50	86.20 $\pm$ 1.50

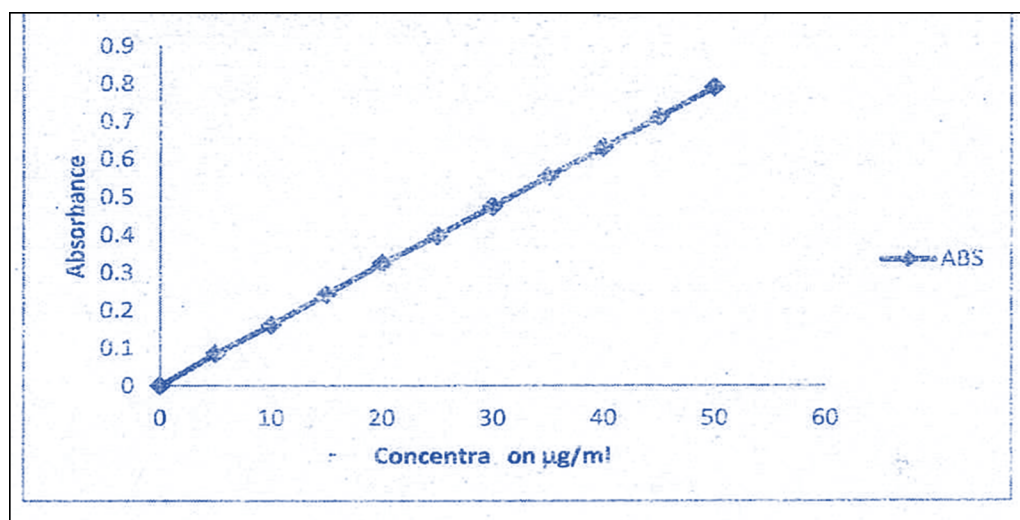
**Table 5 B - VITRO RELEASE PROFILE OF LUFUTIDINE ORODISPERSIBLE TABLETS**

Time in Minutes	Cumulative Percentage drug release $\pm$ SD*					
	F7	F8	F9	F10	F11	F12
5	17.90 $\pm$ 1.04	33.40 $\pm$ 0.29	12.93 $\pm$ 0.23	31.65 $\pm$ 0.20	33.40 $\pm$ 40	59.22 $\pm$ 1.19
10	25.82 $\pm$ 0.45	58.70 $\pm$ 0.18	26.43 $\pm$ 0.54	51.42 $\pm$ 0.46	58.70 $\pm$ 0.18	80.31 $\pm$ 1.18
15	33.24 $\pm$ 1.13	67.13 $\pm$ 0.41	40.61 $\pm$ 0.94	65.89 $\pm$ 1.19	67.13 $\pm$ 0.41	89.67 $\pm$ 0.34
20	43.89 $\pm$ 1.19	78.49 $\pm$ 0.29	55.54 $\pm$ 1.47	76.21 $\pm$ 1.50	78.49 $\pm$ 0.29	91.12 $\pm$ 0.33
25	58.70 $\pm$ 0.41	87.21 $\pm$ 0.44	71.42 $\pm$ 4.61	83.21 $\pm$ 1.42	87.49 $\pm$ 0.44	95.49 $\pm$ 1.41
30	88.87 $\pm$ 1.50	94.05 $\pm$ 0.47	88.55 $\pm$ 1.19	92.38 $\pm$ 0.45	94.05 $\pm$ 0.47	97.79 $\pm$ 0.88

Figure 6  $\lambda$  OF LAFUTIDINE

Lafutidine	
283.20	0.164
215.20	3.088

**Figure 7 CALIBRATION OF LAFUTIDINE IN PHOSPHATE BUFFER pH 6.8**



**Figure 8 FT-IR STUDIES OF LAFUTIDINE**

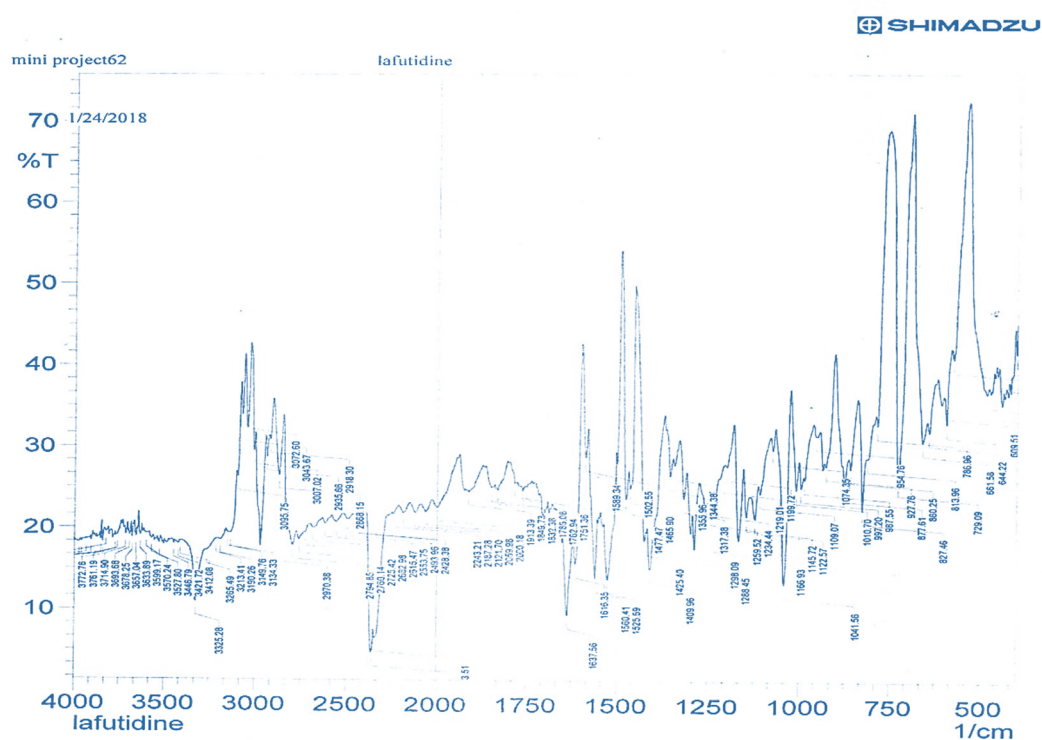




Figure 9 FT-IR STUDIES OF CROSPVIDONE

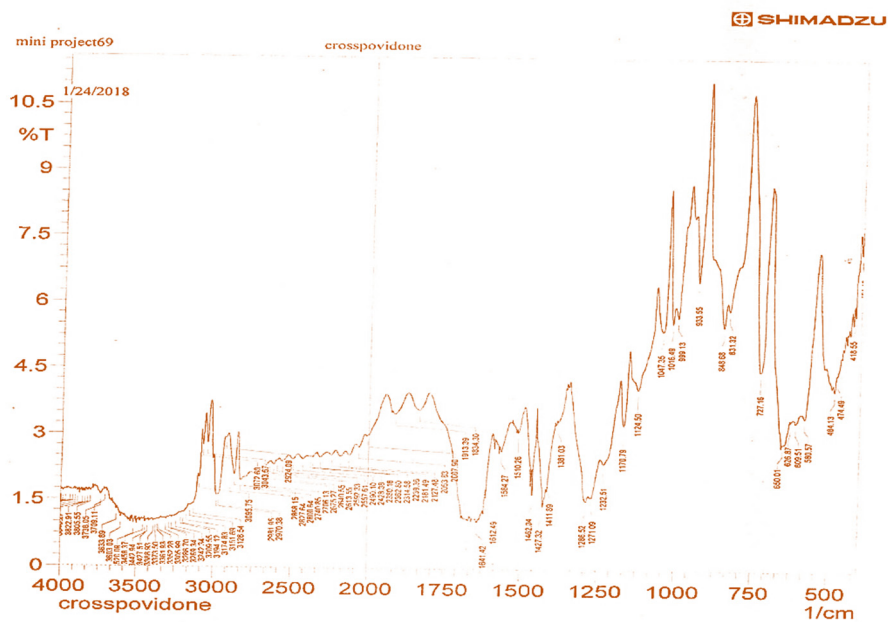


Figure 10 FT-IR STUDIES OF DRUG +CP

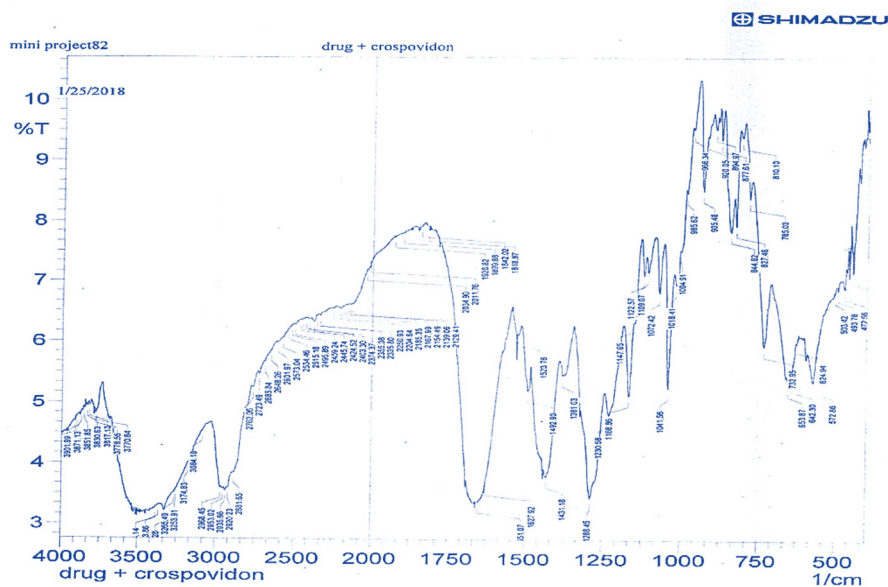


Figure 11 FT-IR STUDIES OF SCMC

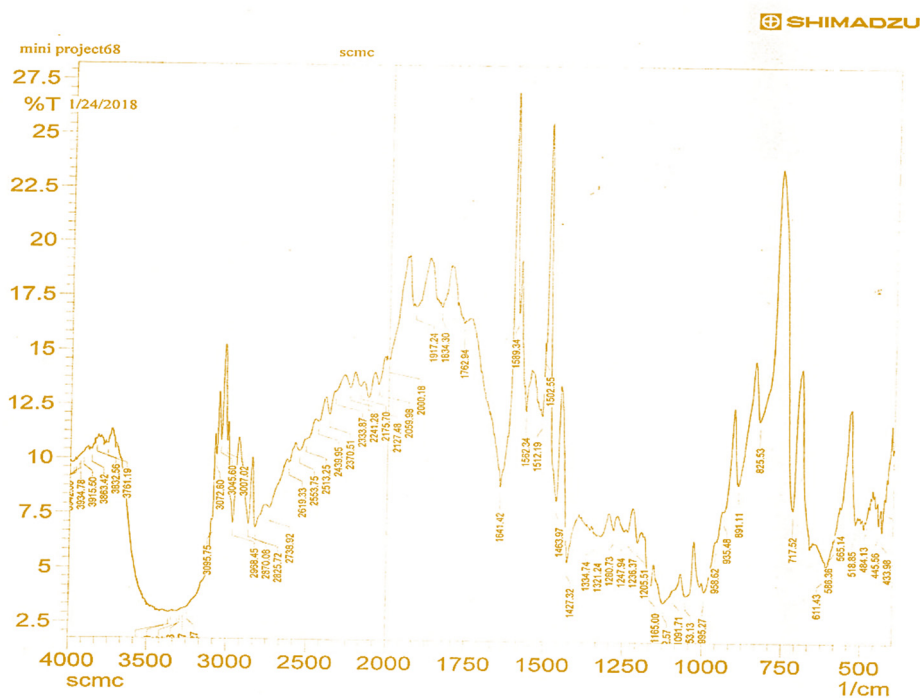
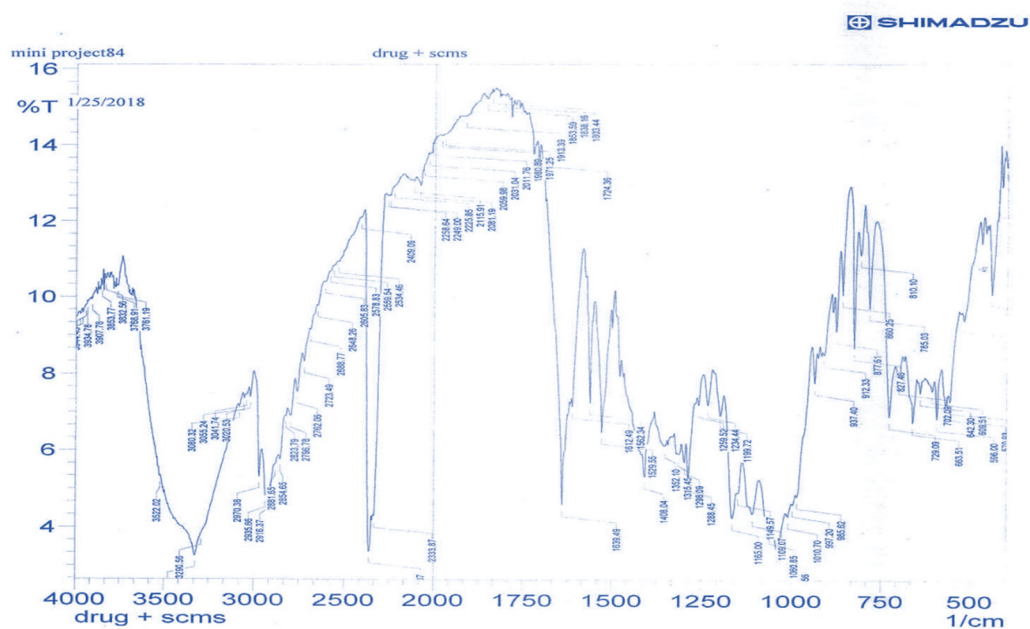


Figure 12 FT-IR STUDIES OF DRUG + SCMC





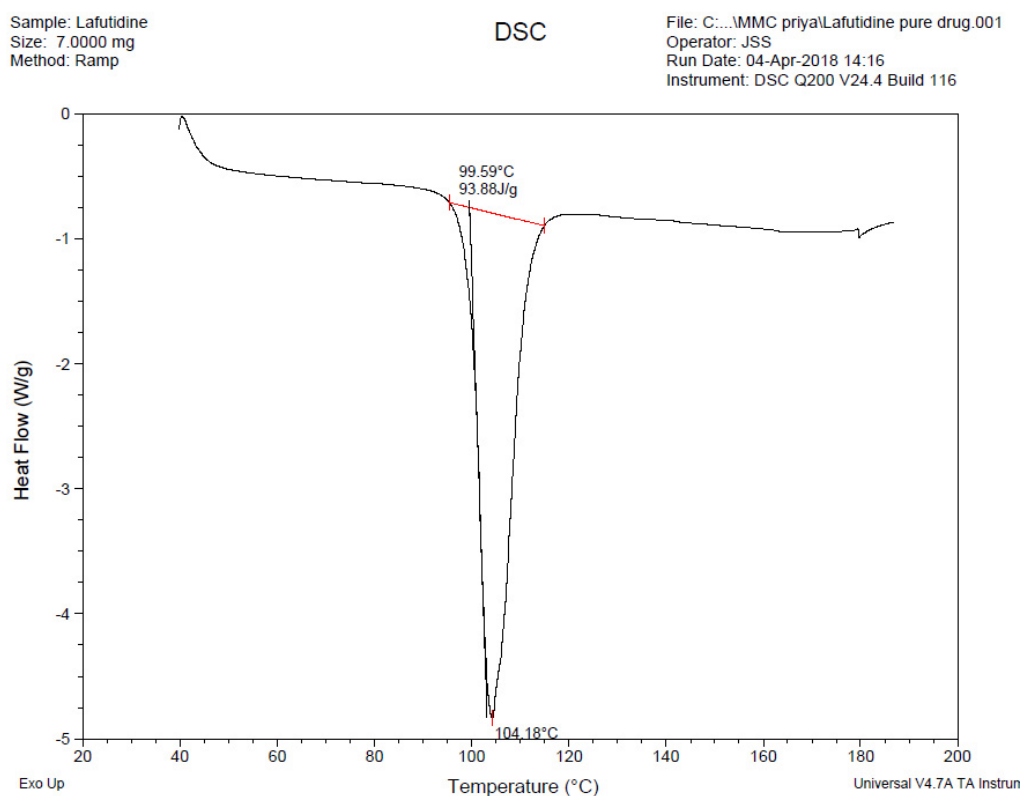
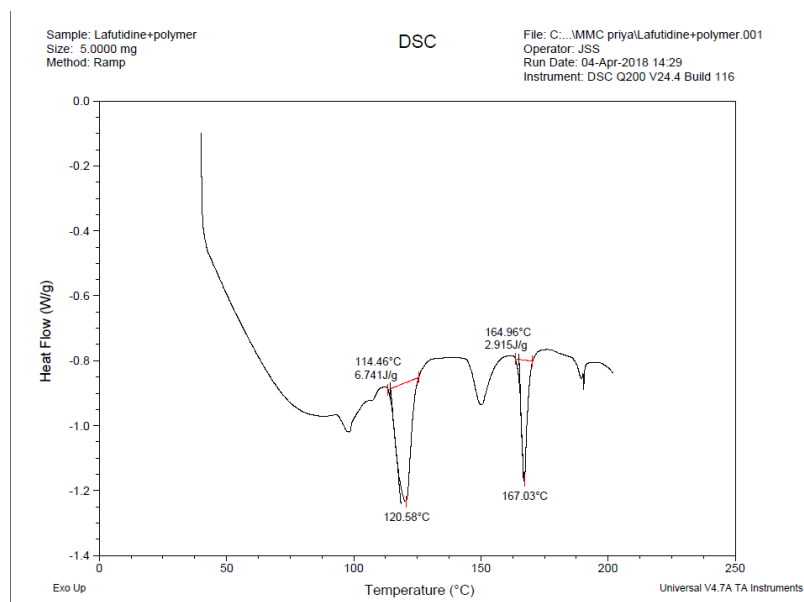
**Figure 15 DSC THERMOGRAM OF LAFUTIDINE****Figure 16 BEST FORMULATION OF LAFUTIDINE**

Figure 17 FORMULATION AND EVALUATION OF MIXED POWDER BLEND

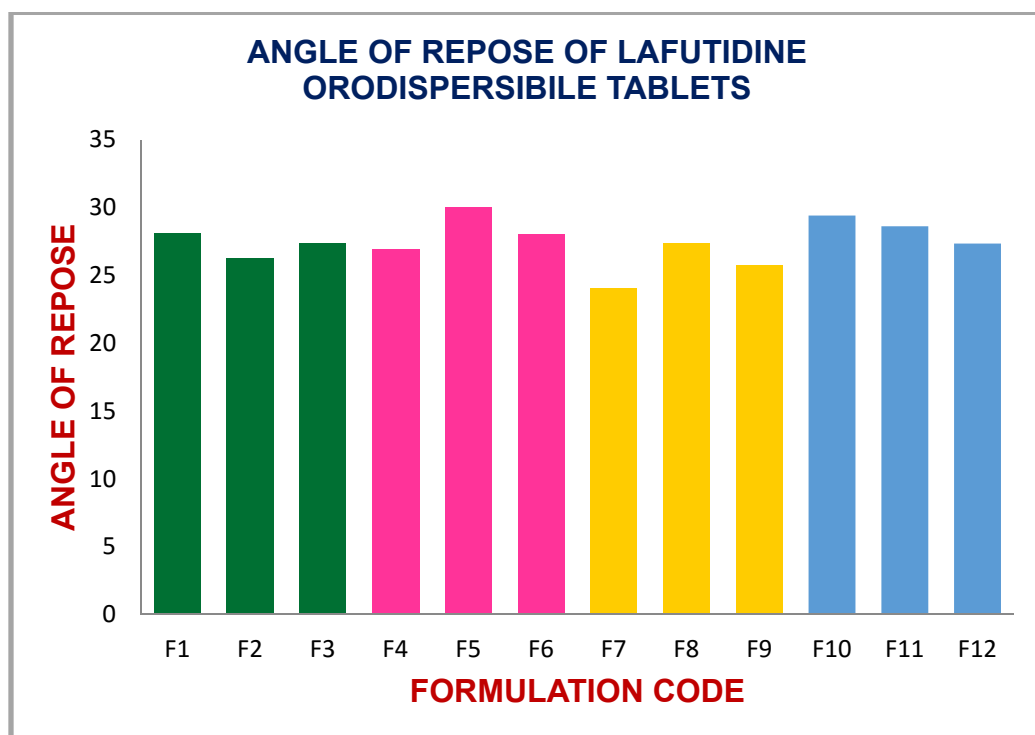


Figure 18

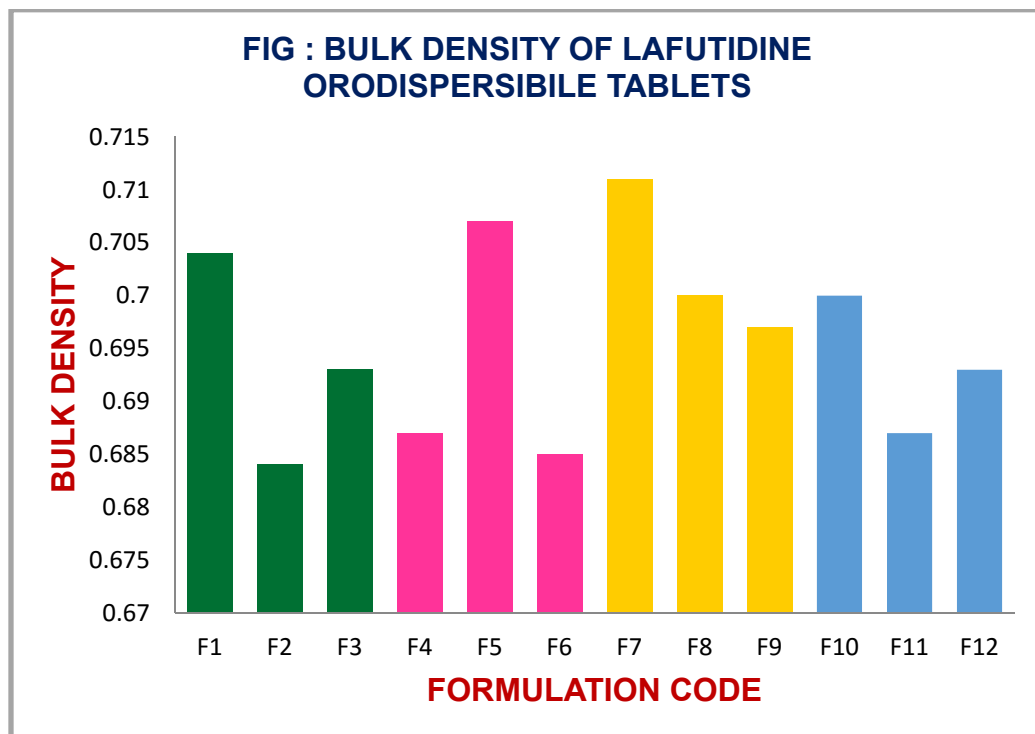


Figure 19

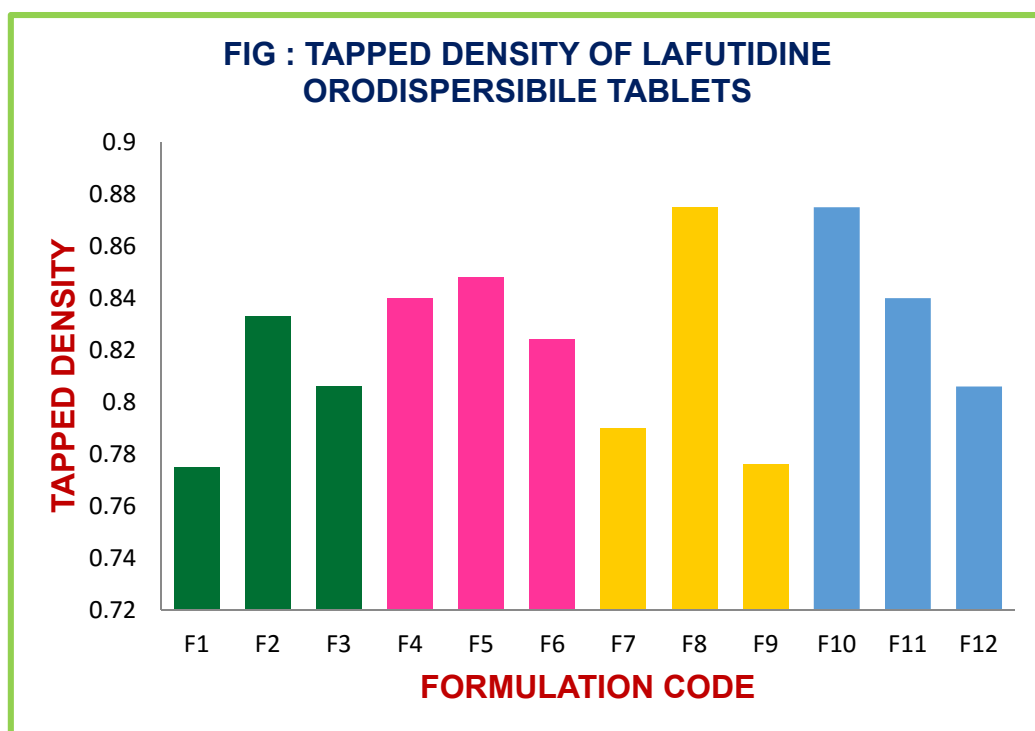


Figure 20

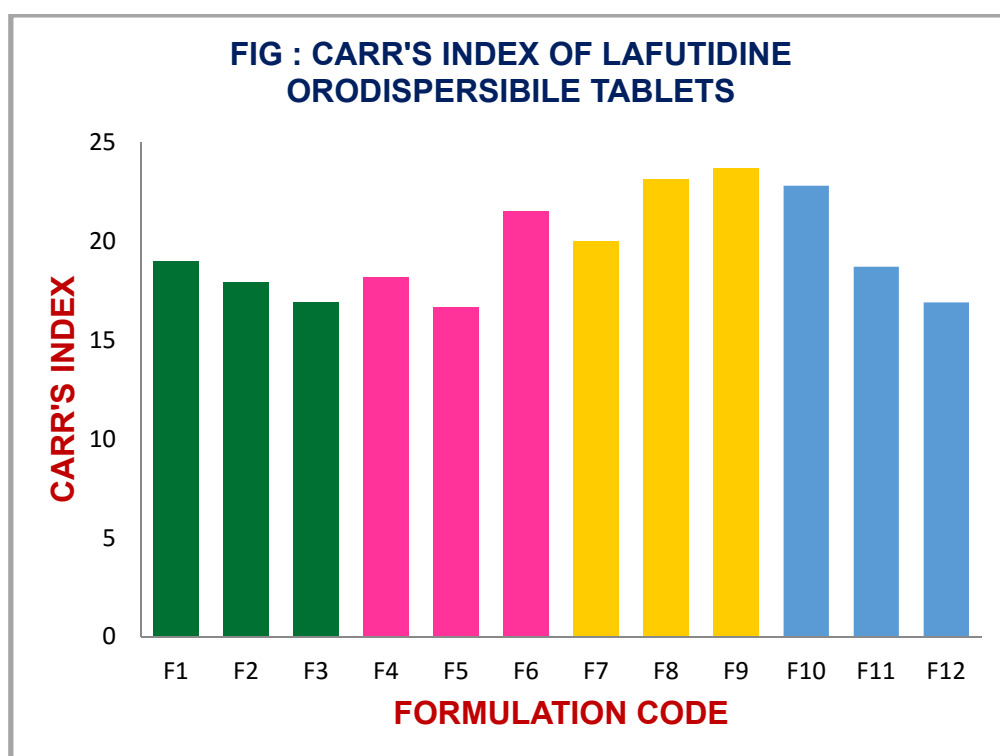


Figure 21

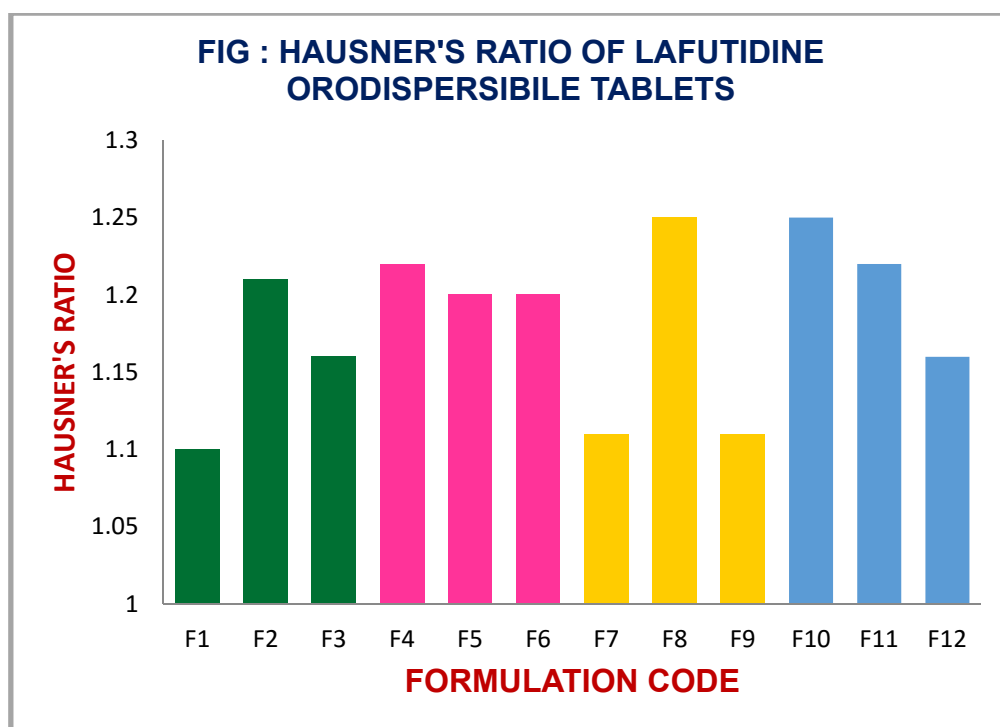


Figure 22

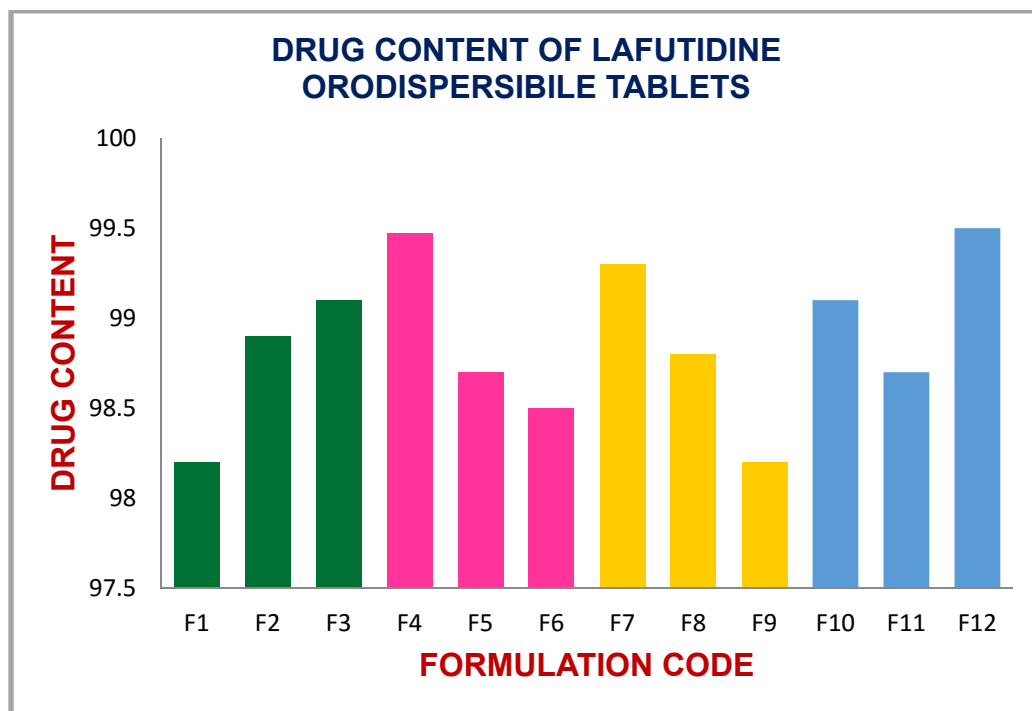


Figure 23

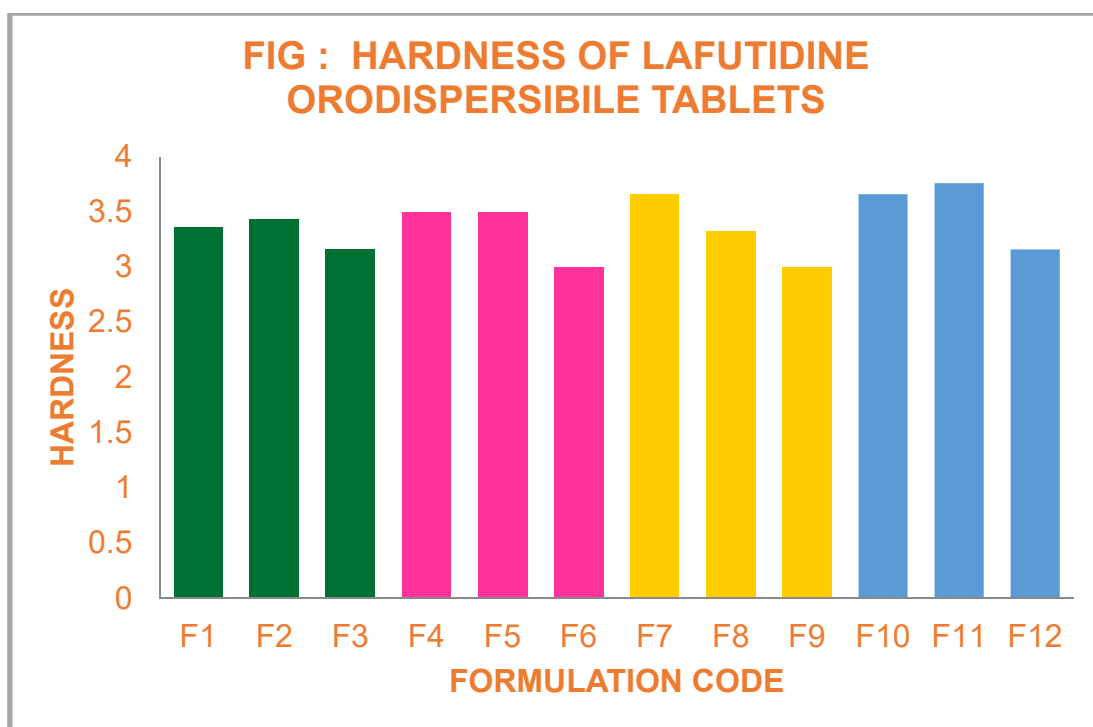


Figure 24

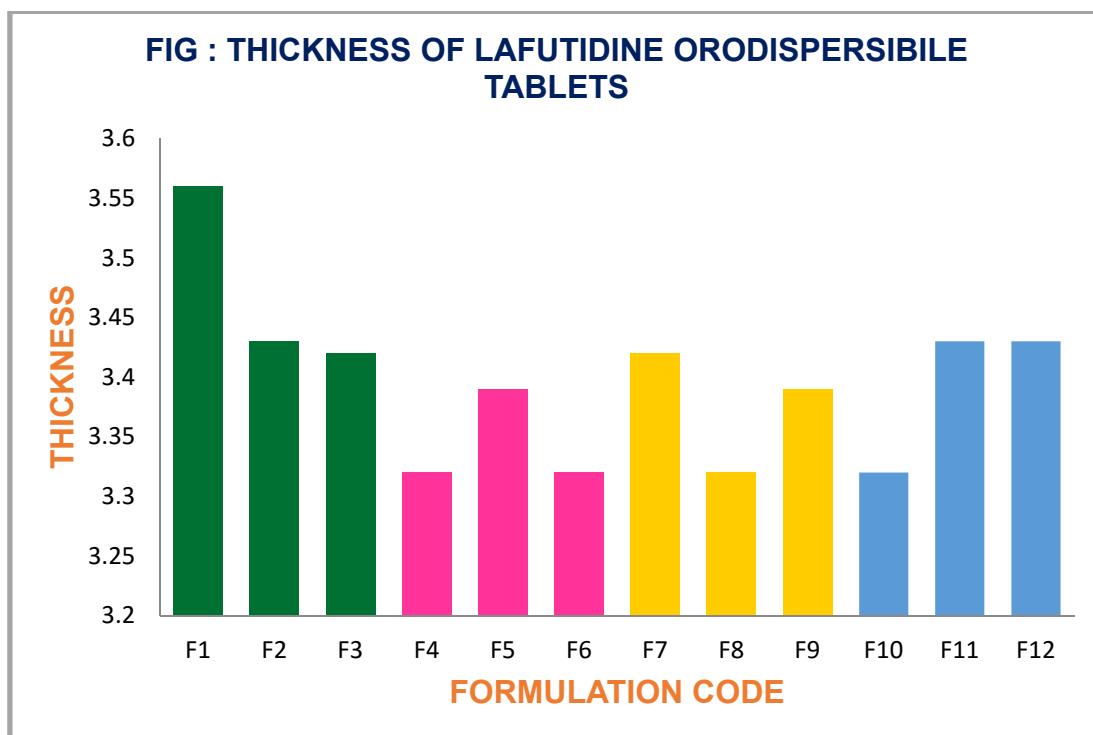




Figure 25

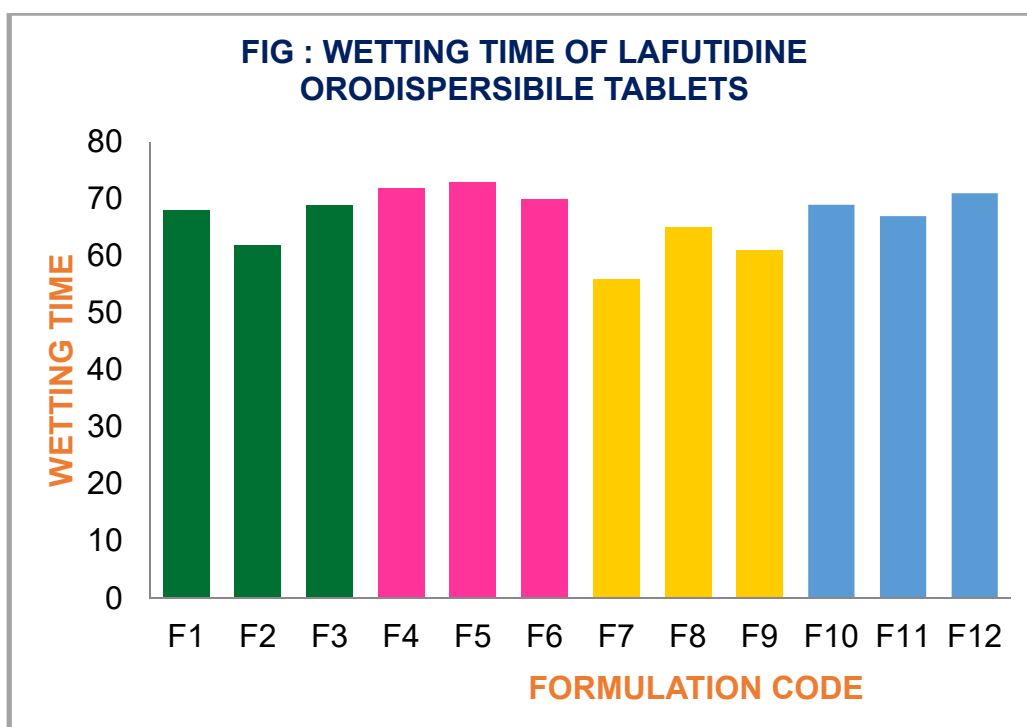


Figure 26

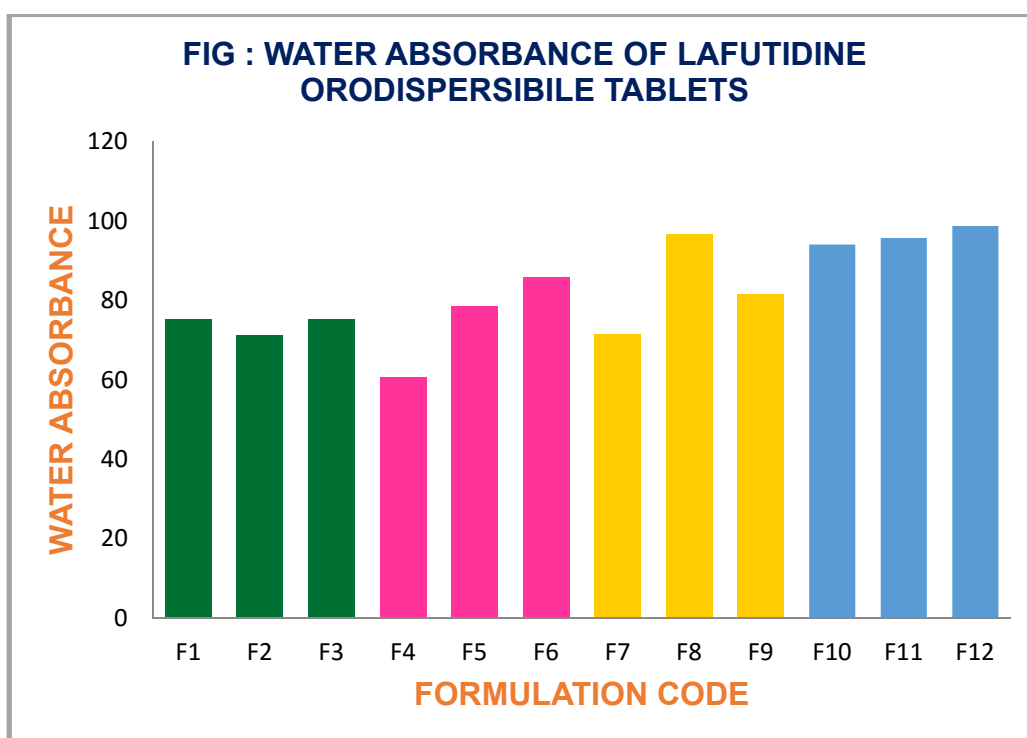


Figure 27

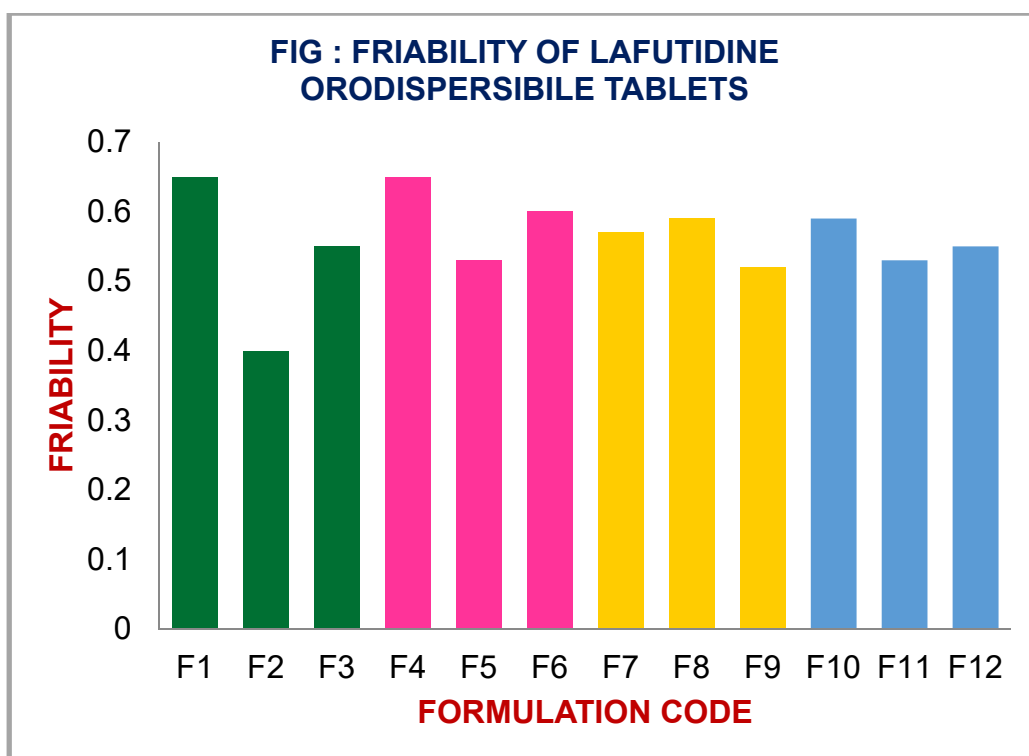


Figure 28

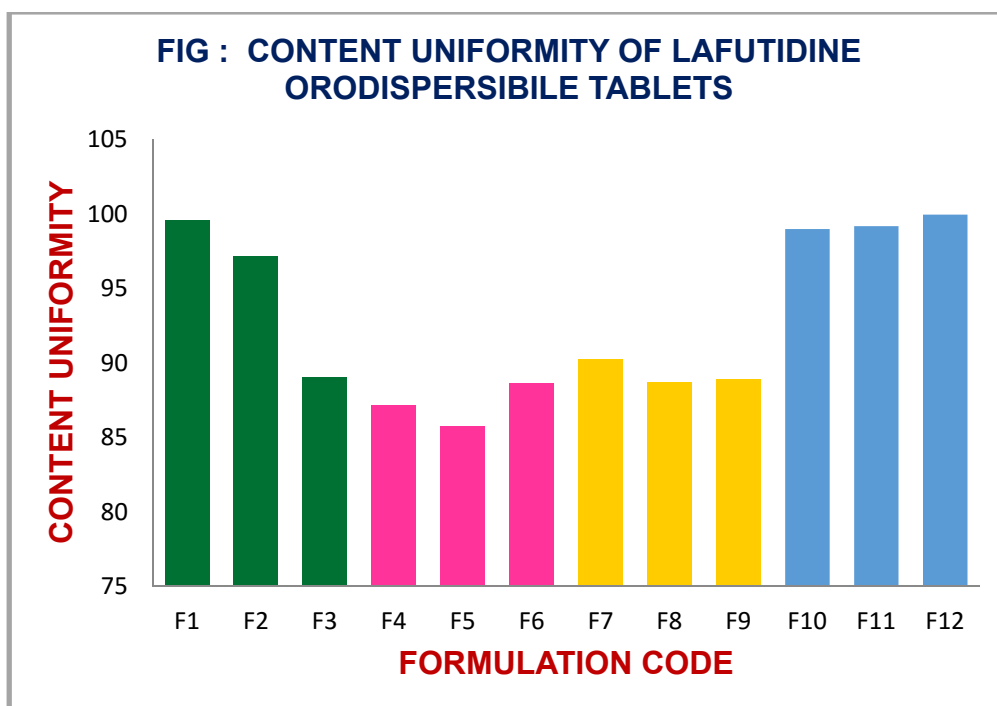


Figure 29

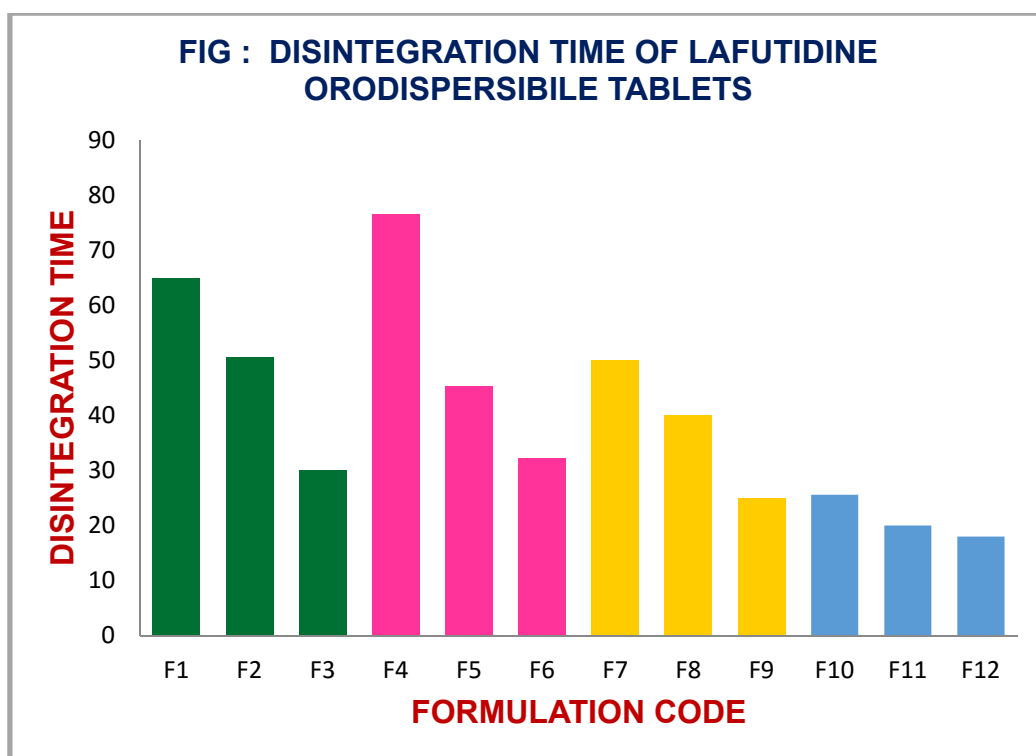


Figure 30

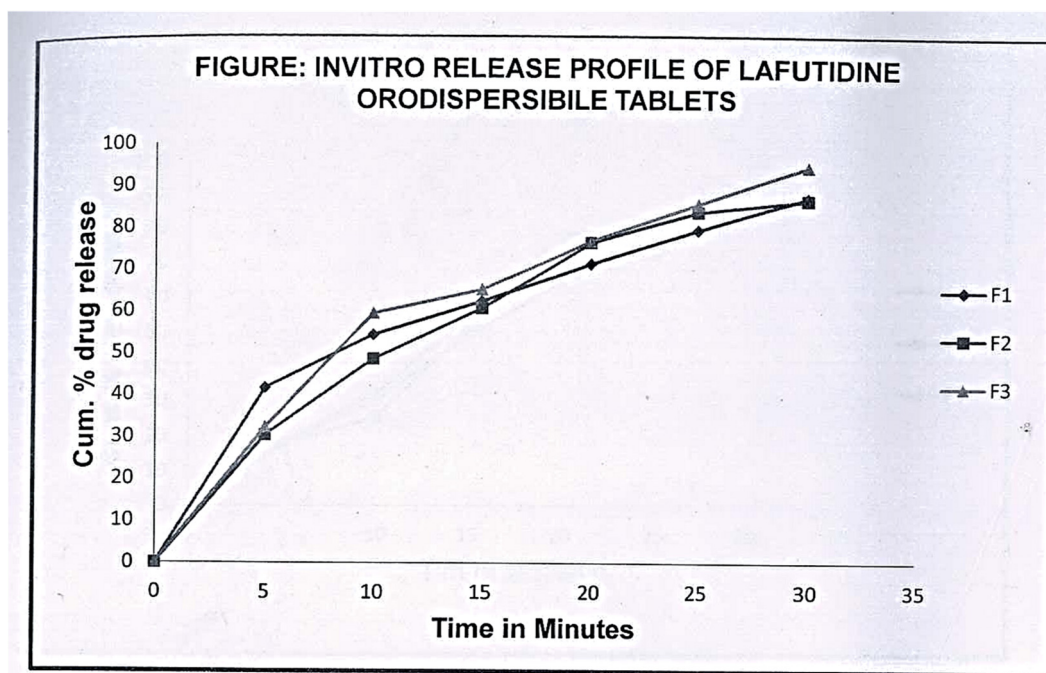


Figure 31

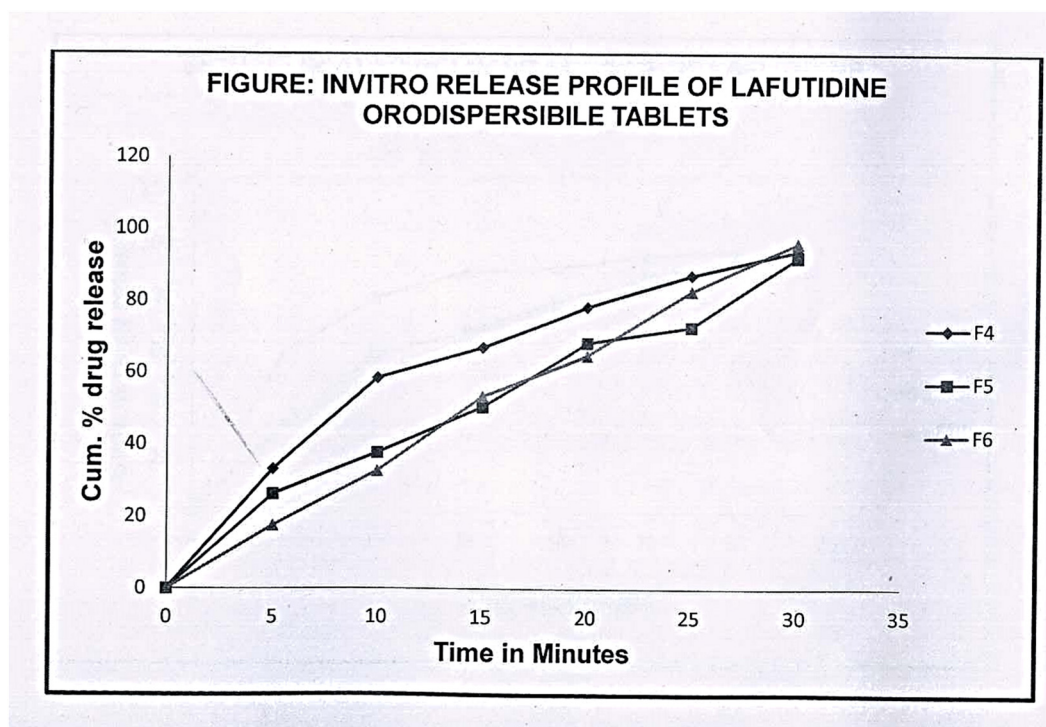


Figure 32

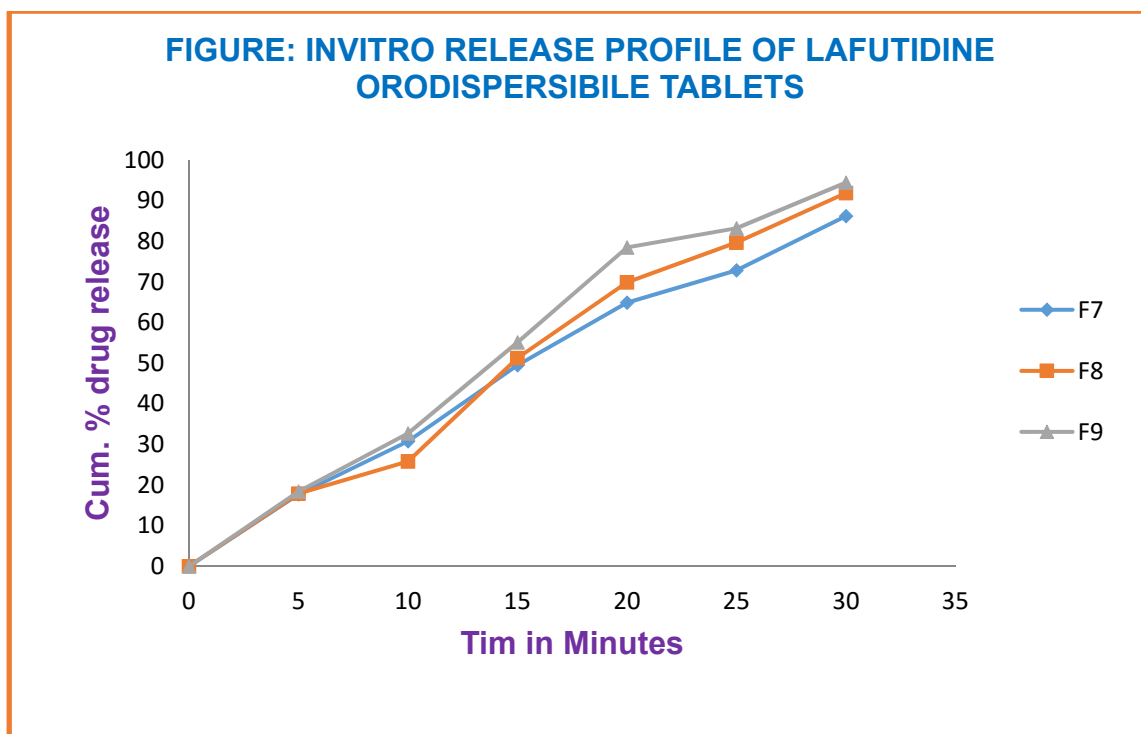
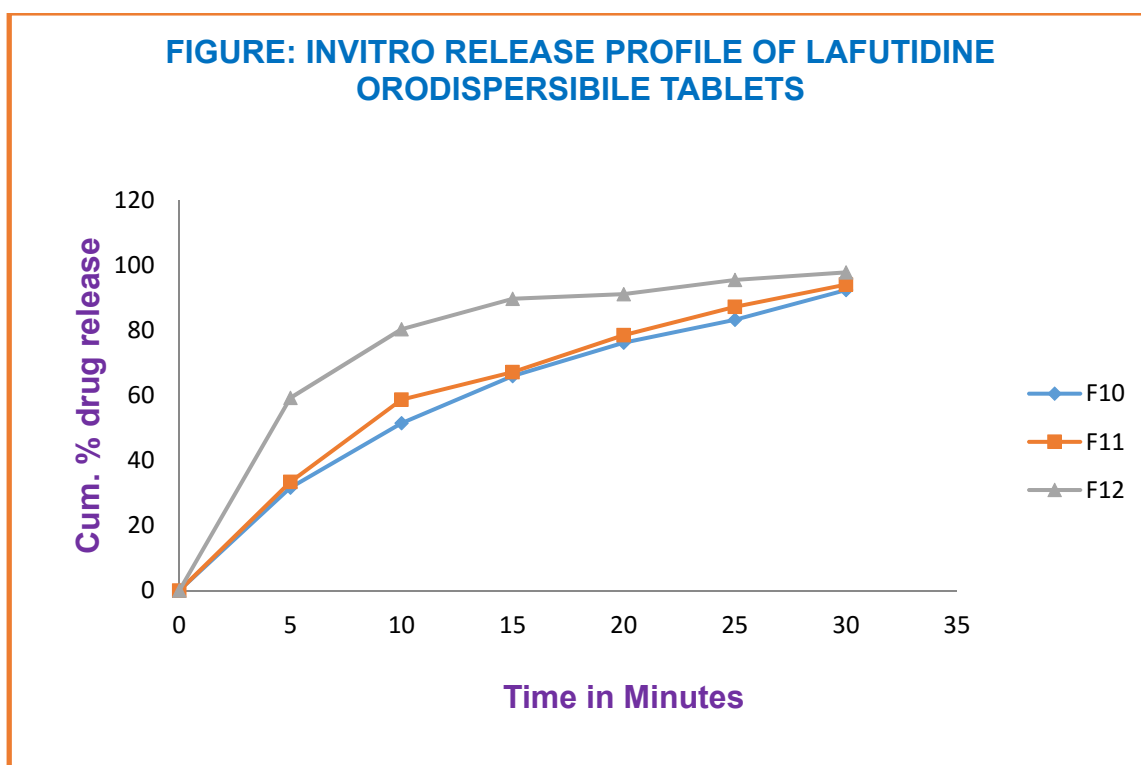


Figure 33



# CHAPTER X

## SUMMARY AND CONCLUSION

## CHAPTER-X

### SUMMARY AND CONCLUSION

- The purpose of the study was to formulate and evaluate oral dispersible tablets of Lafutidine. The results of the Fourier Transmission Infra-red spectroscopy confirm that both drug and excipients are compatible with each other and are devoid of interaction.
- The DSC thermogram of formulation the sharp endothermic peak of pure drug appeared at 99.69°C which reveals that there was no interaction between drug and physical mixture.
- The results of pre compression studies like angle of repose, bulk density, tap density, compressibility index and Hausner's ratio reveals that the prepared powder blends of all formulations possess good flow properties.
- F1, F2, F3 formulations are prepared by using sodium carboxy methyl cellulose in 2%, 3%, 4% respectively. F4, F5, F6 formulations prepared by using croscarmellose super disintegrants in 2%, 3%, 4% respectively. F7, F8, F9 formulation prepared by using pre gelatinized starch super disintegrants in 2%, 3%, 4% respectively. F10, F11, F12 formulation prepared by using combination of sodium carboxy methyl cellulose, croscarmellose, pregelatinized starch in 3%, 4.5%, 12% respectively.
- The prepared tablets were subjected to post compression evaluations and the results indicate that the hardness, thickness and diameter of all

the tablets are uniform, which ensure that all the tablets were of uniform size and shape with good resistance against mechanical damage. The tablets of all formulation contain uniform amount of drug, which ensures content uniformity of tablet formulations.

- The prepared tablets were within the limits of weight variation test, which in turn indicate uniform distribution of contents of the powder blends of each formulation. The friability of all the tablets was found to be <1% which indicates the good mechanical resistance.
- The tablets of all formulation were found to have minimum wetting time and maximum water absorption ratio which is the desired characteristic of oral dissolving tablets which enables faster disintegration of tablets. The disintegration time of all tablets were found to be less than 3 minutes, which ensures faster disintegration except formulation (F1 & F2)



## CONCLUSION

Oro dispersible tablets is a promising approach with a view of obtaining faster action of drug and would be advantageous in comparison to currently available conventional forms. In this study or dispersible tablets of lafutidine were prepared by direct compression method using croscopolvidone, sodium carboxy methyl cellulose and pregelatinized were used in formulation.

Formulation F12 containing 4.5% croscopolvidone has shown the better results for disintegration time of 18 seconds. In-vitro dissolution study showed 97.79% of drug release at the end of 30 minutes. From the study, it can be conclude that the oro- dispersible tablet of lafutidine could perform better bioavailability, effectiveness and hence better patient compliance.

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